Use and Limitations of *In Vitro* Dissolution Testing: Topic Introduction and Overview

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Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

In Vitro Dissolution Testing: Objectives

- Assure batch to batch quality
- Guide development of new formulations
- Provide “process control” and quality assurance
- Ascertain the need for bioequivalence studies
  - Different strengths
  - Post-approval changes
  - Multi-source products

Dissolution Testing: Issues

- Dissolution testing can be “non-discriminating”.
- Dissolution testing can be “over discriminating”.
- Products that dissolve about 70% in 45 minutes often have no medically relevant bioequivalence problems.
- Dissolution testing (especially only a single point criterion) is often not sufficient to assure product quality/ bioavailability.
- Demonstration of *in vitro-in vivo* correlation (IVIVC) is necessary.
- IVIVC’s are “Product Specific”.

Desired Future State of *In Vitro* Dissolution Testing

- Sensitive enough to detect relevant product changes so as to ensure the quality and consistent performance of products
- Predictive of *in vivo* performance of drug products and thus reduce unnecessary human studies, accelerate drug development, and hasten evaluation of post-approval changes

Uses and Limitations of *In Vitro* Dissolution Testing

- Use and Limitations of *In Vitro* Dissolution Testing: Topic Introduction and Overview — Lawrence Yu
- Dissolution Testing: Evolving Dissolution Apparatus — Cindy Buhse
- Dissolution Testing: Evolving Dissolution Media for Predicting *In Vivo* Performance — Arzu Selen
- Oral Bioperformance & 21st Century Dissolution Testing — Gregory Amidon
- Dissolution Testing and Quality-by-Design — Lawrence Yu
- Followed by:
  - Topic Wrap-up and Future Directions
  - Questions to the Committee/Committee Discussion

Dissolution Testing: Evolving Dissolution Apparatus

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 8, 2012

Cindy Buhse, Ph.D., Director
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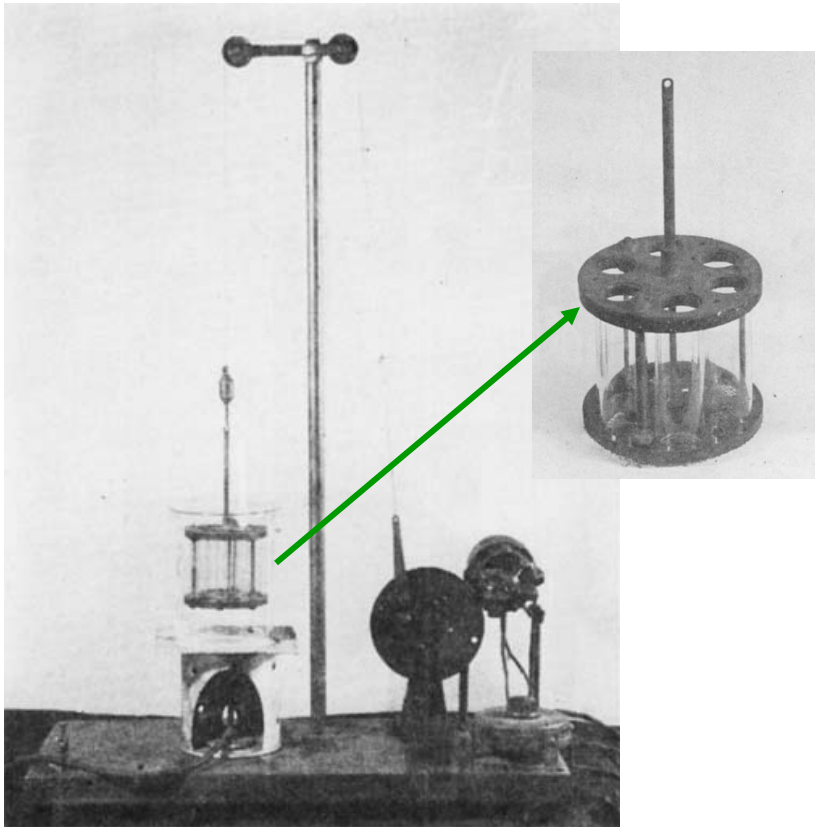
Division of Pharmaceutical Analysis
Center for Drug Evaluation and Research
US Food and Drug Administration

Dissolution Testing Evolves from Disintegration Test

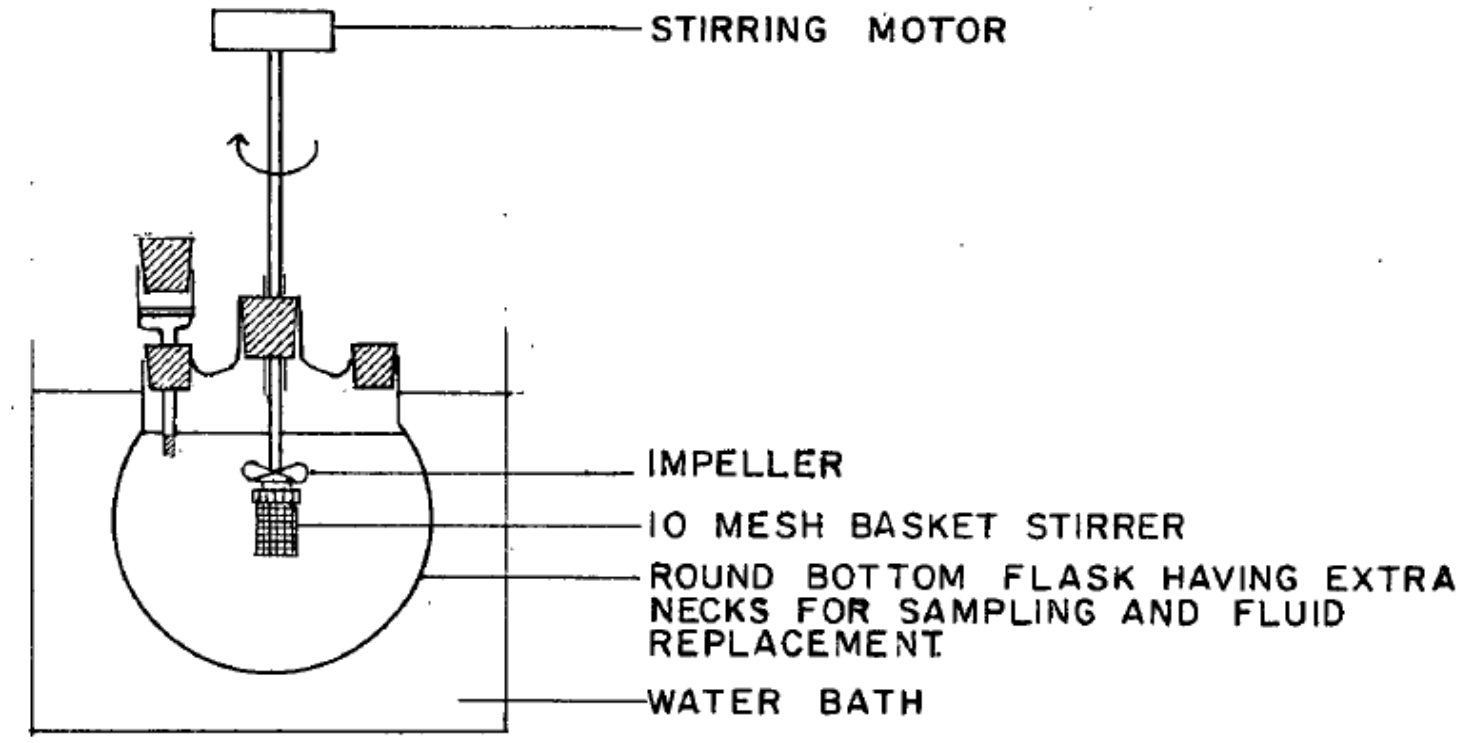


Stoll-Gershberg disintegration apparatus

- Convenient and sensitive chemical analyses weren't available in 1950s.
- Official disintegration tests were adopted in 1945 by the British Pharmacopoeia and in 1950 by the USP.
- However, disintegration was recognized as an **incomplete test** as evidenced by the 1950 USP-NF statement that "disintegration does not imply complete solution of the tablet or even of its active ingredient".

GERSHBERG S, STOLL FD, 1946, Apparatus, for tablet disintegration, and for shaking-out extractions, Journal of the American Pharmaceutical Association, 35(9), 284-7.

A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 – Basket Method

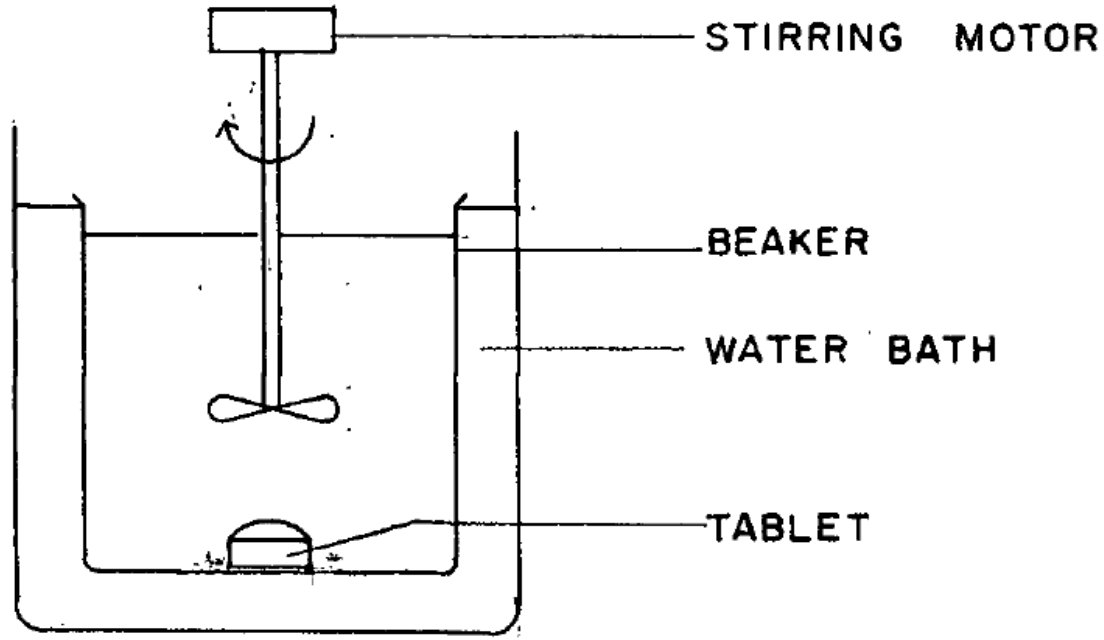


Basket Stirrer Method

Searl and Pernarowski, 1967

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 – Paddle Method

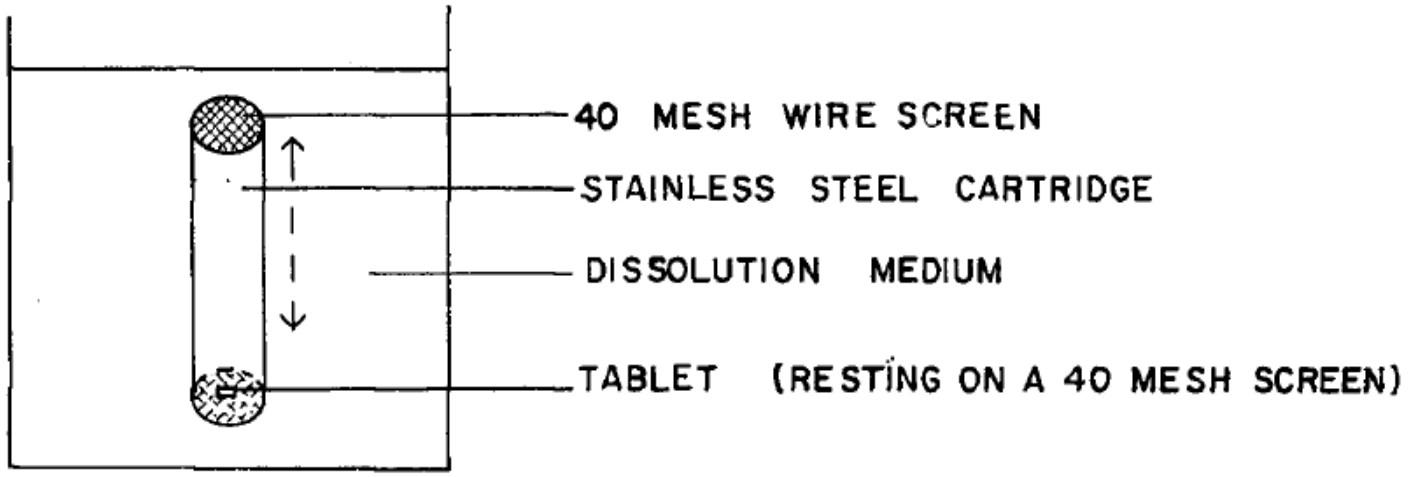


(A) Beaker Method

Levy-Hayes, 1960

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 -- Reciprocating Cylinder Method

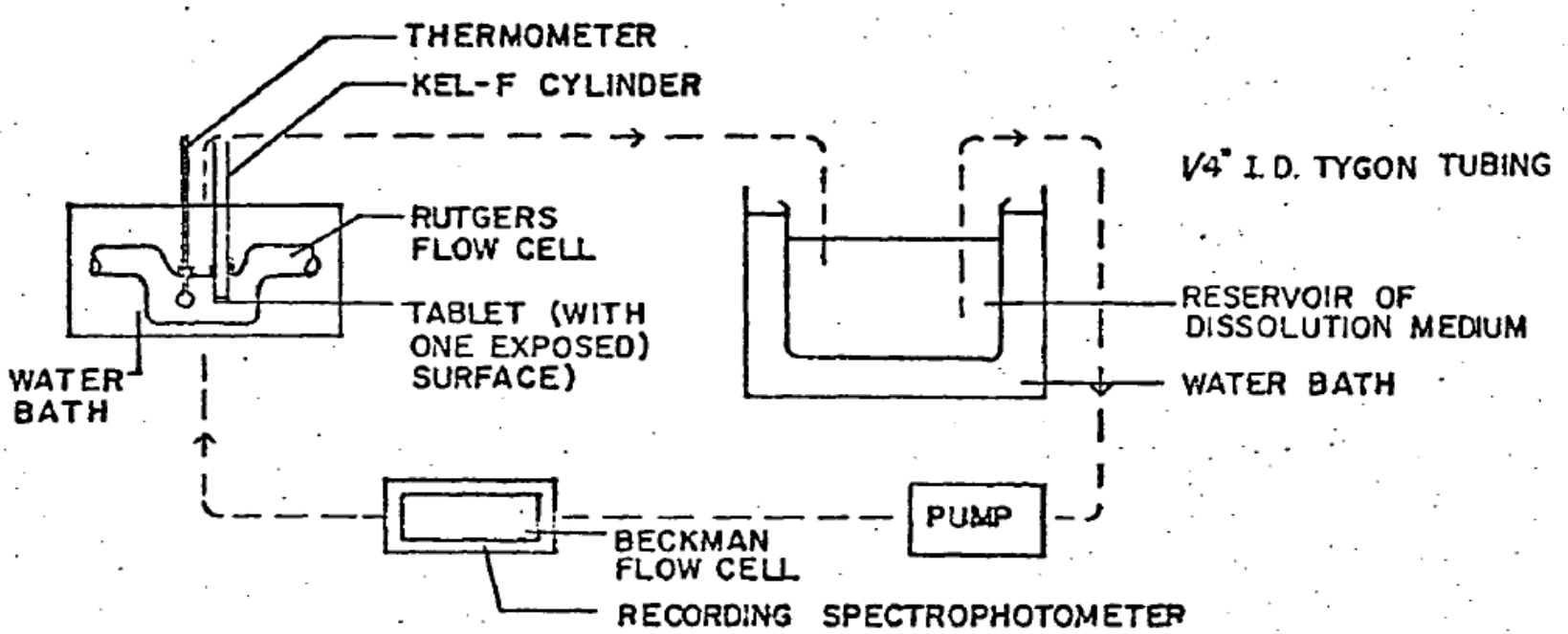


(A) Vliet's Method

Vliet, 1959

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 – Flow-through Method



(D) Apparatus of Lapidus and Lordi.

Lapidus and Lordi, 1966

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

The First USP Dissolution Apparatus 1, Basket

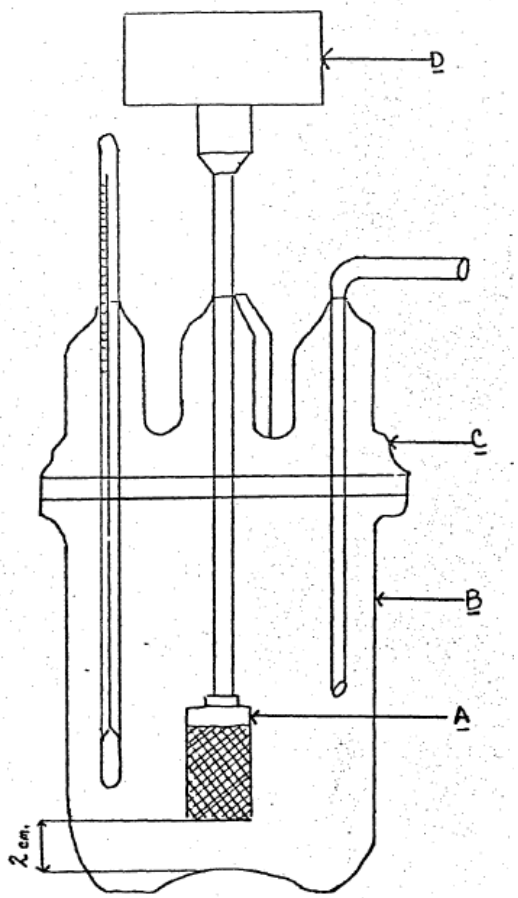
USP Apparatus 1

A – Basket

B – 1000ml resin flask

C – Cover

D – High-torque stirring motor

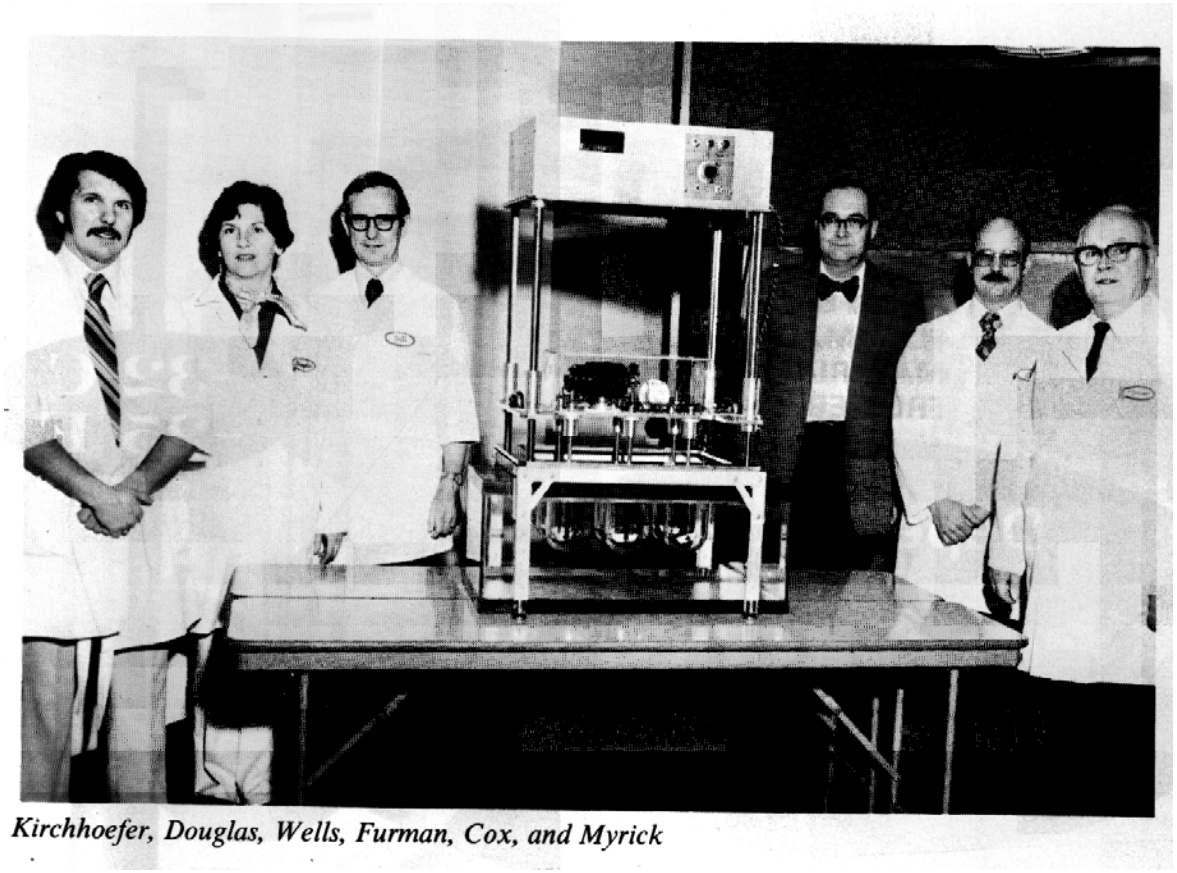


1970 - Dissolution test, apparatus 1 (basket), USP 18

1976 - Dissolution test, apparatus 2 (paddle), USP 19

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

Early Dissolution Testing in a FDA Lab in 1970s



Kirchhoefer, Douglas, Wells, Furman, Cox, and Myrick

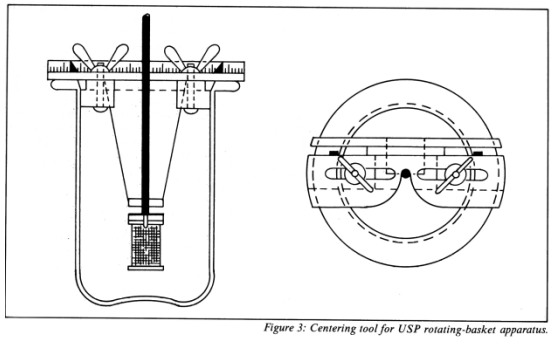
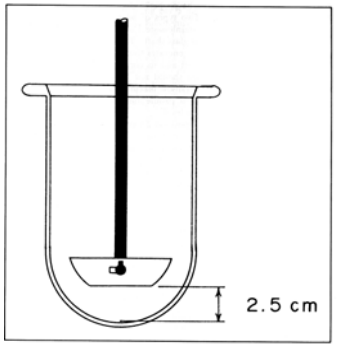


Figure 3: Centering tool for USP rotating-basket apparatus.

USP rotating-basket apparatus and a centering tool



USP paddle apparatus

Pharmaceutical Technology, April, 1978, Vol 2, 16-53

FDA's Definition and Views on Dissolution Testing in 1970's

- *In vitro* dissolution testing as applied to solid-dosage drug forms measures the amount of drug dissolved in a known volume of liquid medium at a predetermined time, using a specified apparatus designed to carefully control the parameters of dissolution testing.
- *In vitro* dissolution testing can help pinpoint formulations that may present potential bioequivalence problem.
- Once a formulation has been shown to be bioavailable, dissolution testing is of great value in assuring lot-to-lot bioequivalence.

Don C. Cox, Carol C. Douglas, William B. Furman, Ross D. Kirchhoefer, James W. Myrick and Clyde E. Wells, 1978, Guidelines for dissolution testing, Pharmaceutical Technology, Vol 2, No.4, 41-53

FDA's Concerns and Standpoint on Dissolution Testing in 1970's

- Dissolution tests are critical and difficult to carry out properly. Care and attention must be given to those aspects that have been identified as crucial. It is our hope that other scientists will share their findings and techniques so that dissolution testing may be advanced to a reproducible and reliable scientific procedure.
- If labs can not be expected to agree on the results of a dissolution test, then an IVIVC obtained by one lab can not be generalized as being valid in all labs.
- Differences between dissolution results obtained in industrial labs and those obtained in agency labs raise problems in the making of regulatory decisions.

Don C. Cox, Carol C. Douglas, William B. Furman, Ross D. Kirchhoefer, James W. Myrick and Clyde E. Wells, 1978, Guidelines for dissolution testing, Pharmaceutical Technology, Vol 2, No.4, 41-53

USP Monographs for Dissolution Testing

Table 1
Number of monographs in the US Pharmacopeia and the National Formulary which require dissolution or release tests

Edition/year	Monographs for immediate-release dosage forms	Monographs for modified-release dosage forms	
		Extended	Delayed
USP 18-NF 13/1970	6	–	–
USP 19-NF 14/1975	12	–	–
USP 20-NF 15/1980	60	–	–
USP 21-NF 16/1985	400	1	–
USP 22-NF17/1990	462	18	5
USP 23-NF18/1995	501	6	25
USP 24-NF19/2000	552	26	14
USP 29-NF24/2006	619	38	14

Aristides Dokoumetzidis, Panos Macheras, 2006, Historical Perspectives: A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System, International Journal of Pharmaceutics, 321, 1–11

FDA's Guidances for Dissolution Testing

1978 – FDA/DPA published a guideline for dissolution testing

1984 – FDA/DPA published the "Guidelines for dissolution testing: an addendum"

1995 – Guidance for Industry, SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence

1997 – Guidance for Industry, SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence

1997 – Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms

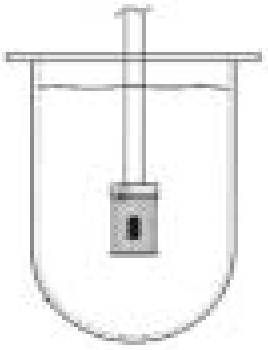
1997 – Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

2010 – Guidance for Industry, The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)

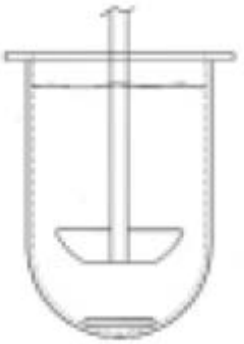
2011 – Guidance for Industry, Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions, Annex 7(R2) Dissolution Test General Chapter

Current Official USP Dissolution Apparatuses

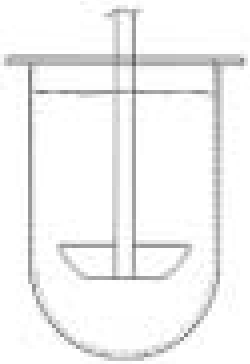
Apparatus	Samples	Test Parameters
Apparatus 1 (Basket)	Immediate-release, extended-release, and delayed-release dosage forms.	Temperature, rotation speed, dissolution medium
Apparatus 2 (Paddle)	Immediate-release, extended-release, and delayed-release dosage forms.	Temperature, rotation speed, dissolution medium
Apparatus 5 (Paddle over disk)	Primary use is for semi-solid topical dosage forms but has also been used for drug release and skin/membrane permeation for transdermal patches.	Temperature, rotation speed, dissolution medium
Apparatus 6 (Cylinder)	Transdermal system.	Temperature, rotation speed, dissolution medium



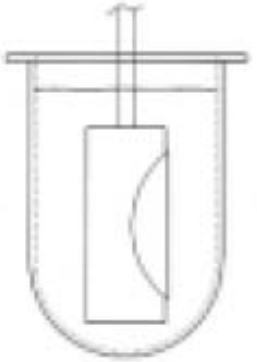
USP 1 (basket)



USP 5 (paddle over disk)



USP 2 (paddle)



USP 6 (cylinder)

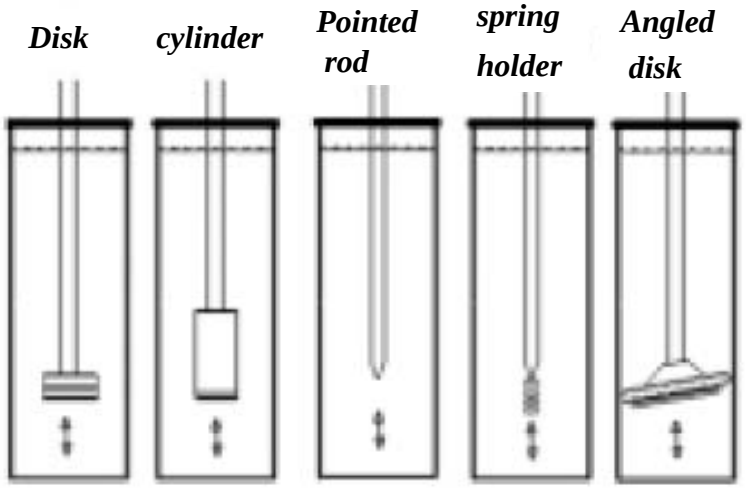
Pictures copied from website, http://www.protechcro.com/images/01Dissolution.pdf, accessed July 2, 2012

Current Official USP Dissolution Apparatuses

Reciprocating Apparatus is typically used for imitating the pH changes that occur in the body and is suited for extended and sustained release dosage forms.

Apparatus	Samples	Test Parameters
Apparatus 3	Immediate-release, extended-release, and delayed-release dosage forms.	Temperature, dip rate, dissolution medium.
Apparatus 7	Transdermal system, extended-release dosage forms (coated tablet)	Temperature, dip rate, dissolution medium

USP 3 - reciprocating cylinder



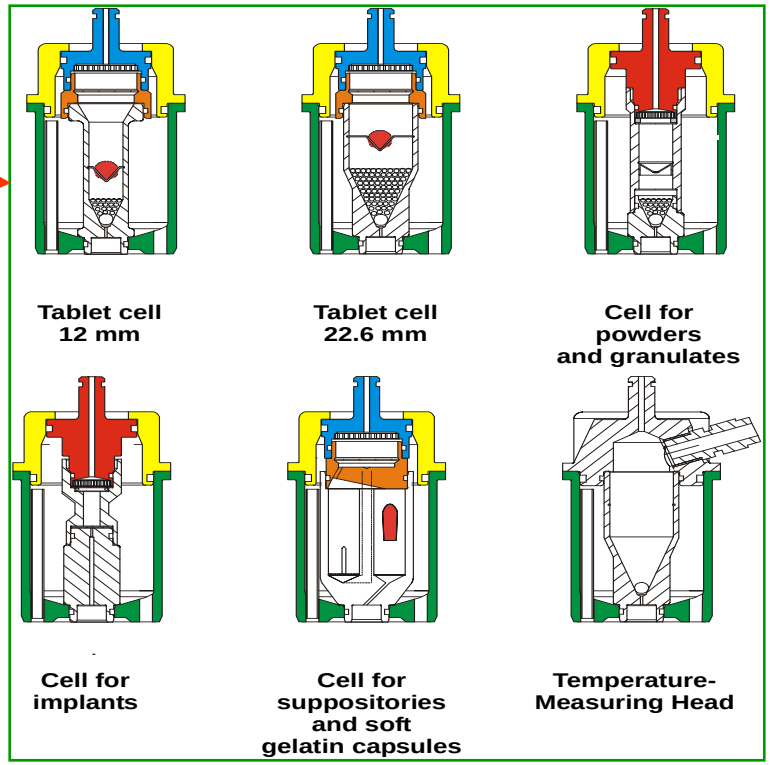
USP 7 - reciprocating holder

Pictures copied from website, http://www.protechcro.com/images/01Dissolution.pdf, accessed July 2, 2012

Current Official USP Dissolution Apparatuses

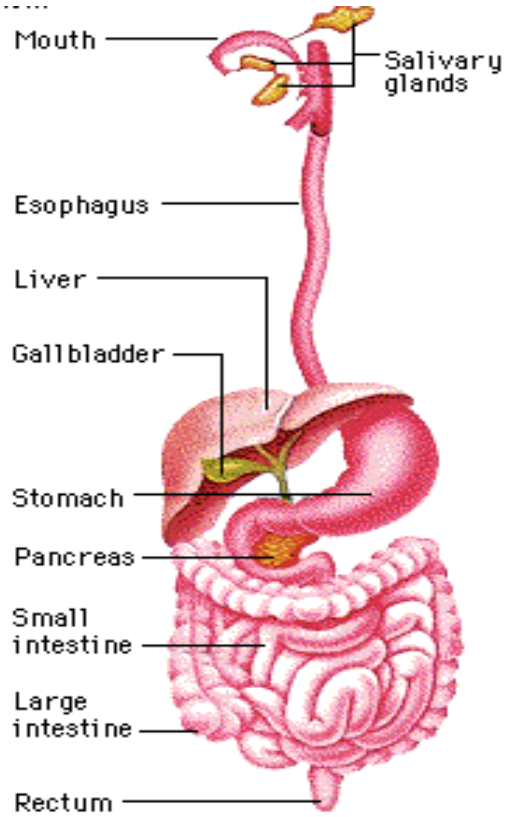
USP 4 – flow through

Samples	Test Parameters
Immediate-release, extended-release, and delayed-release dosage forms. tablets, capsules, suppositories, powders, drug eluting stents, creams, gels, suspensions etc.	Temperature, flow rate, pulses per minute, dissolution medium

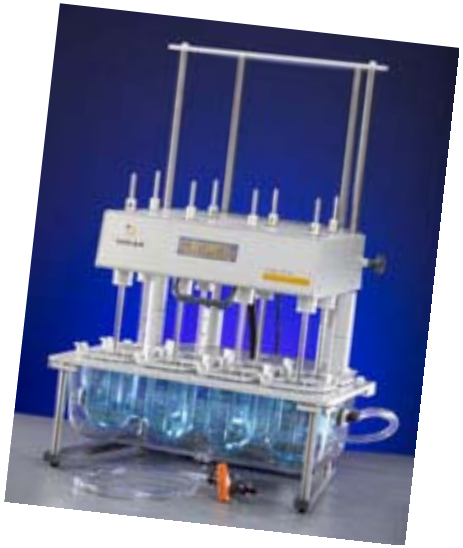


Pictures copied from website, http://www.sotax.com/USP-4-Semi-automated-systems.127.0.html, accessed July 2, 2012

Does Current Dissolution Method Have Any Biological Relevance?



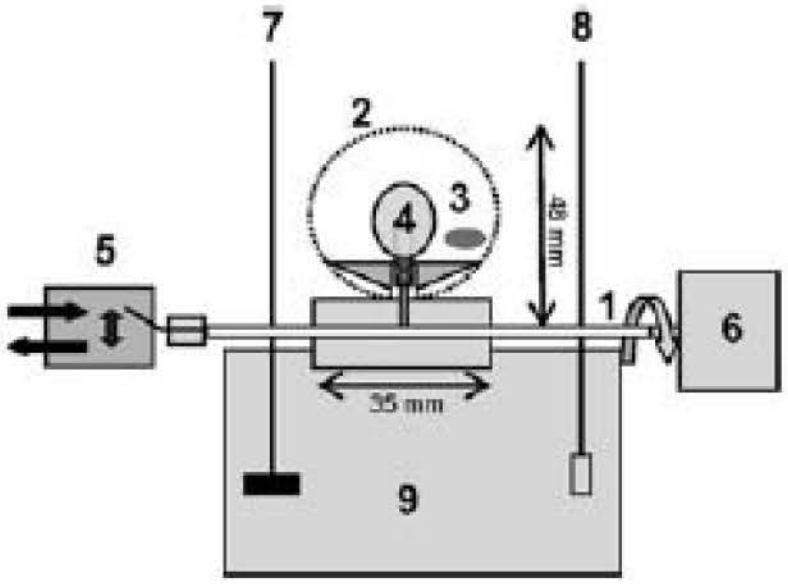
- Disintegration
- Solids transfer
- Dissolution
- Changing pH
- Food and drink
- Absorption
- Clearance



Picture copied from website, ***http://www.google.com/images?q=digest+system&hl=en&gbv=2&tbm=isch&ei=uZQZUIT4O-ju0gHx8oCYAg&start=20&sa=N, accessed July 30, 2012***

Picture copied from website, http://www.protechcro.com/images/01Dissolution.pdf, accessed July 2, 2012

New Designs for Dissolution Testing



1. Central axis (ø 8 mm)
2. Chamber (ø 35 mm mesh size 0.5 mm, wire 0.1 mm)
3. Dosage form
4. Inflatable balloon
5. Solenoid valves
6. Stepping motor
7. Stirrer (paddle 15*35 mm^2)
8. Sampling
9. Standard vessel

Fig. 1. Schematic representation of the dissolution stress test device.

Garbacz, G. et al. Irregular absorption profiles observed from diclofenac extendedrelease tablets can be predicted using a dissolution test apparatusthat mimics in vivo physical stresses. *Eur. J. Pharm. Biopharm.* 2008, *70* (2), 421–428.

New Designs for Dissolution Testing

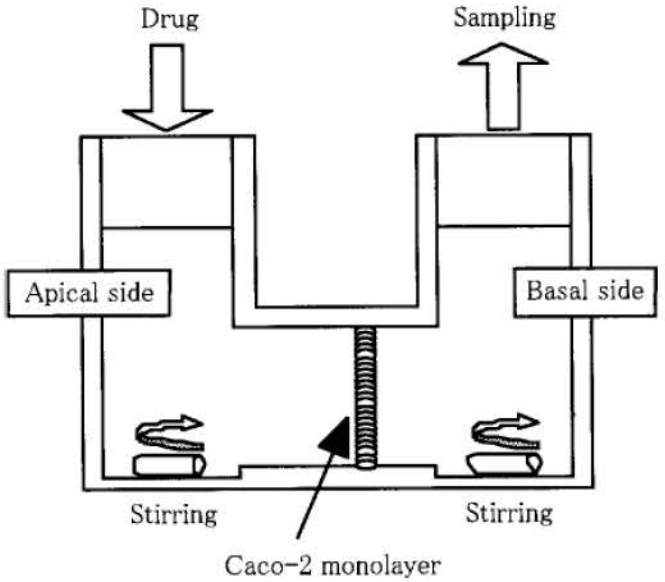
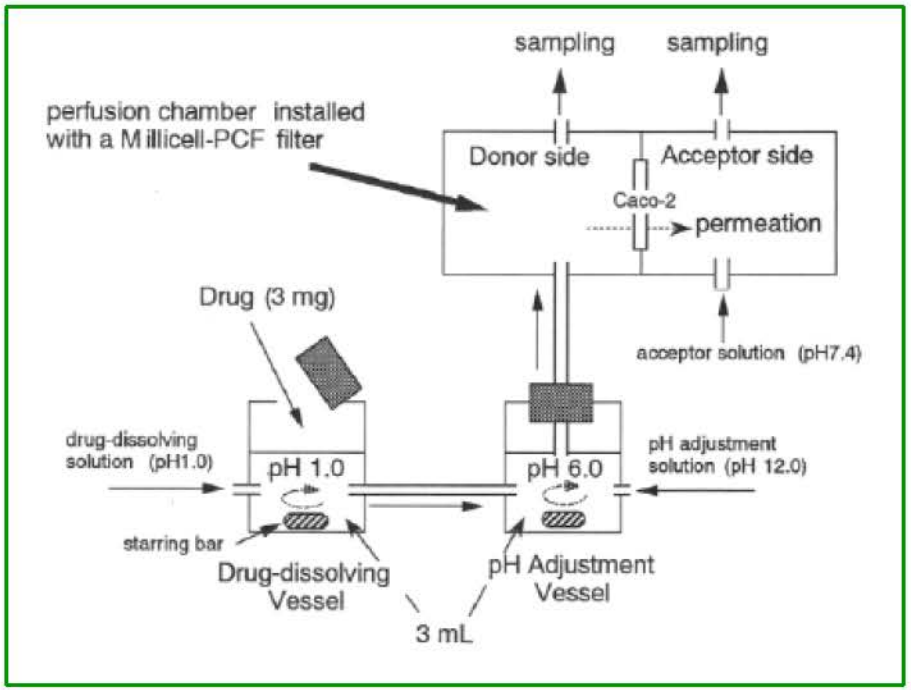


Fig. 1. Schematic illustration of the dissolution/permeation system (D/P system). Caco-2 monolayer was mounted between the apical and basal chambers. Both sides of the monolayer were filled with transport medium (apical side; pH = 6.5, volume = 8 ml, basal side; pH = 7.4, volume = 5.5 ml) and stirred by magnetic stirrers constantly. Drugs were applied to the apical side as solid, suspension, or solution.

Makoto KATAOKA et al. 2011, *In Vitro Dissolution/Permeation System to Predict the Oral Absorption of Poorly Water-Soluble Drugs: Effect of Food and Dose Strength on It, Biol. Pharm. Bull. 34*(3) 401—407



M. Kobayashi et al. International Journal of Pharmaceutics 221 (2001) 87–94

New Designs for Dissolution Testing

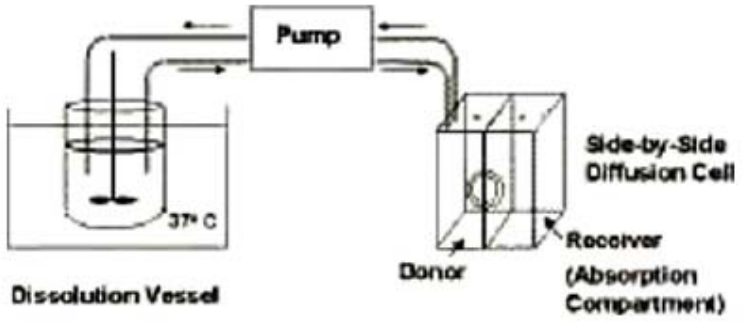
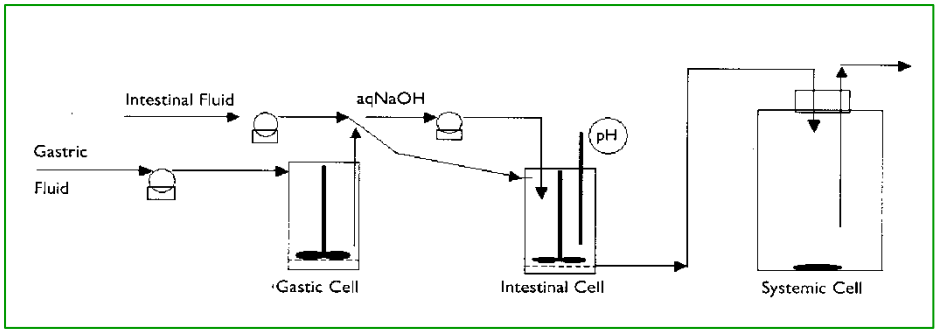
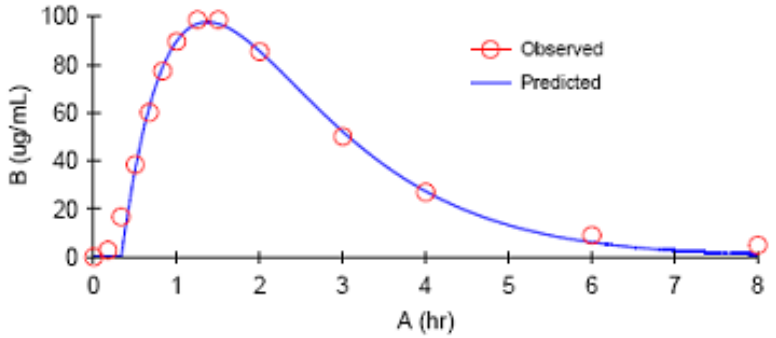


Figure 1. Schematic of the continuous dissolution/Caco-2 system.



- Hank's Balanced Salts Solution (HBSS) at pH 6.8 was used as the dissolution medium, in order to accommodate the Caco-2 monolayer.
- SGF and deionized water do not support Caco-2 cell viability.
- The dissolution testing time is limited by Caco-2 cells for less than 2 hours.



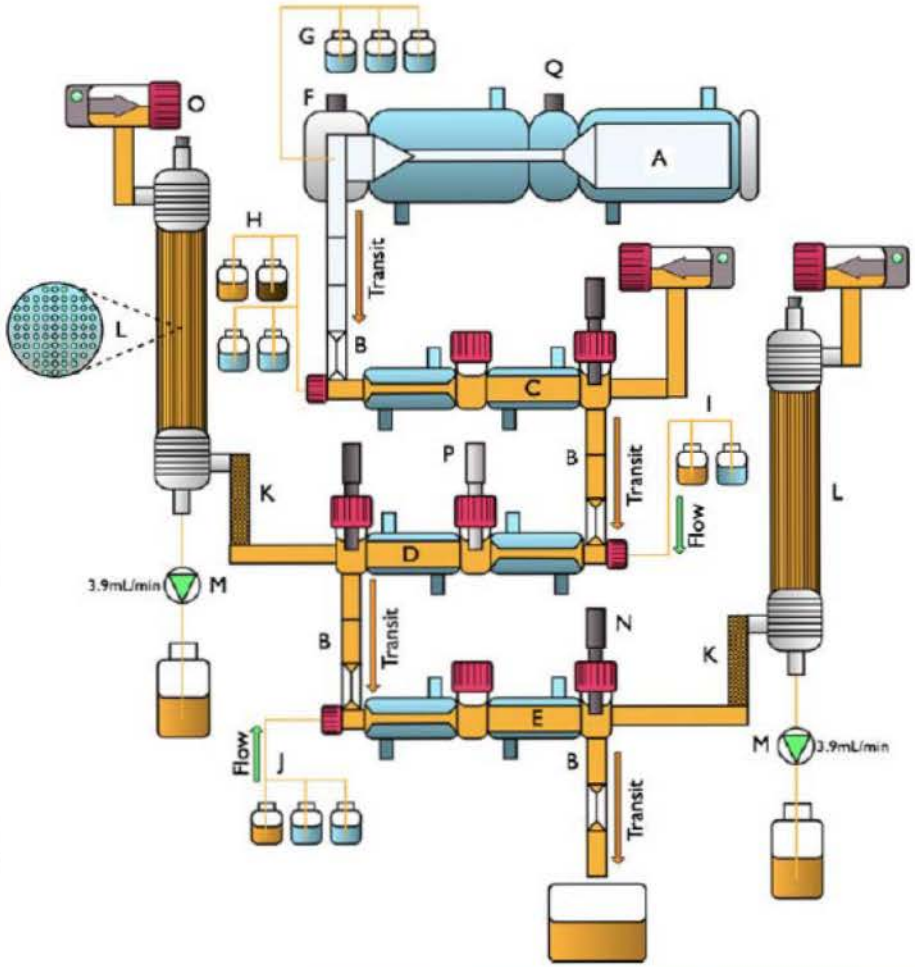
Mark J. Ginski, Rajneesh Taneja, and James E. Polli, 1999, Prediction of Dissolution-Absorption Relationships from a Continuous Dissolution/Caco-2 System, *AAPS Pharmsci, 1 (3) article 3*

L. Hughes et al. Dow Apparatus (FloVitro)

New Designs for Dissolution Testing

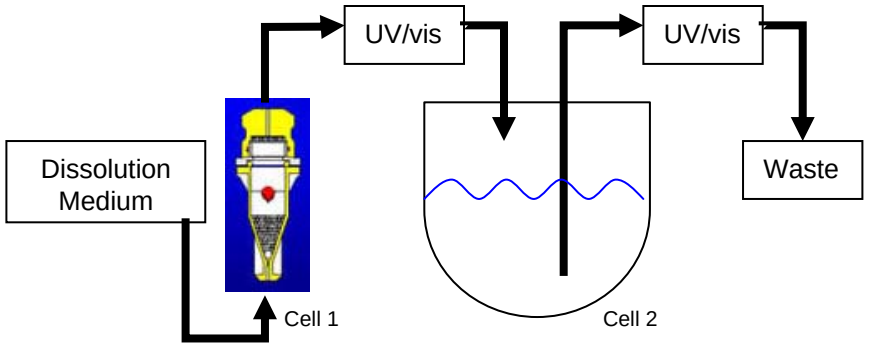
TNO TIM-1 System Schematic

A	Stomach Compartment
B	Peristaltic Valve
C	Duodenum Compartment
D	Jejunum Compartment
E	Ileum Compartment
F	Pressure Sensor
G	Stomach Secretion
H	Duodenum Secretion
I	Jejunum Secretion
J	Ileum Secretion
K	Pre-Filter
L	Semi-Permeable Membrane
M	Filtrate Pump
N	pH Electrode
O	Level Sensor
P	Temperature Sensor
Q	Dosing Port



Paul A. Dickinson, et al. An Investigation into the Utility of a Multi-compartmental, Dynamic, System of the Upper Gastrointestinal Tract to Support Formulation Development and Establish Bioequivalence of Poorly Soluble Drugs. The AAPS Journal, Vol. 14, 196-205, 2012.

New Designs for Dissolution Testing



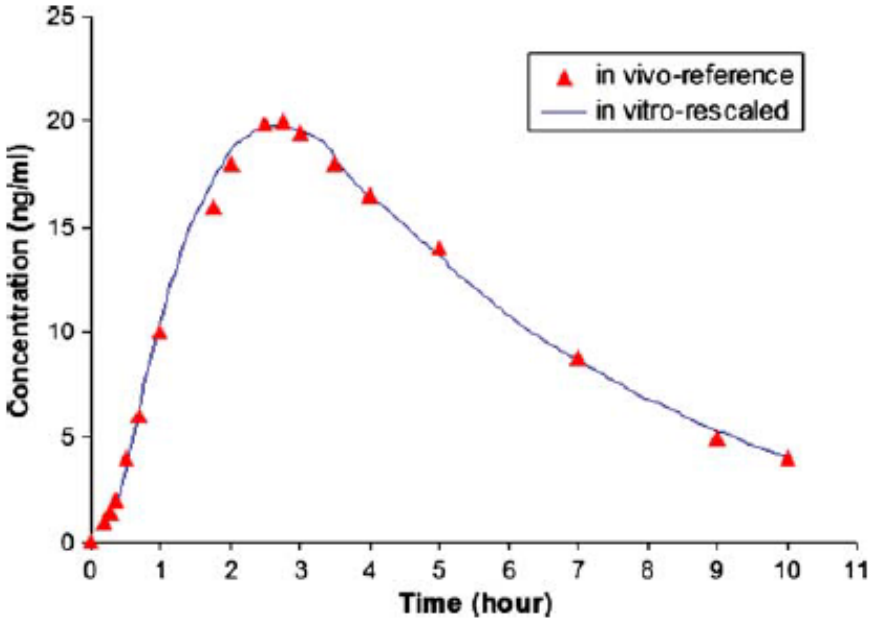
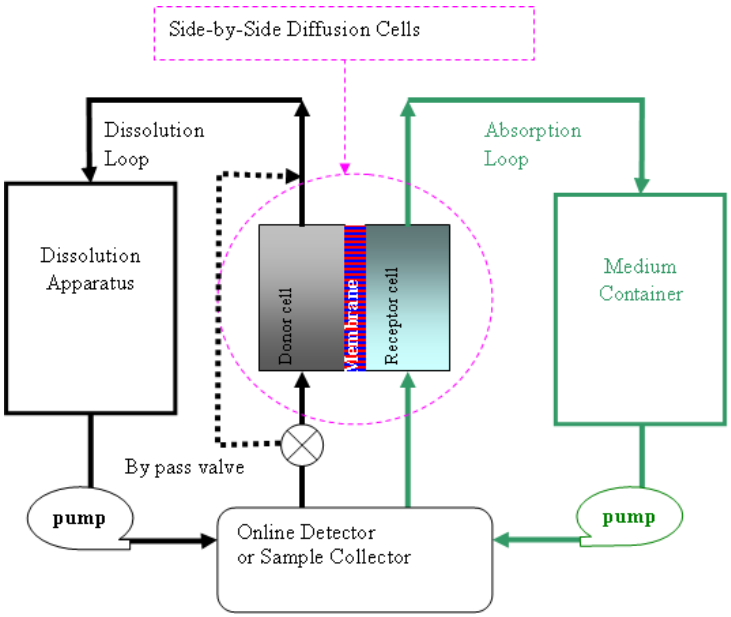


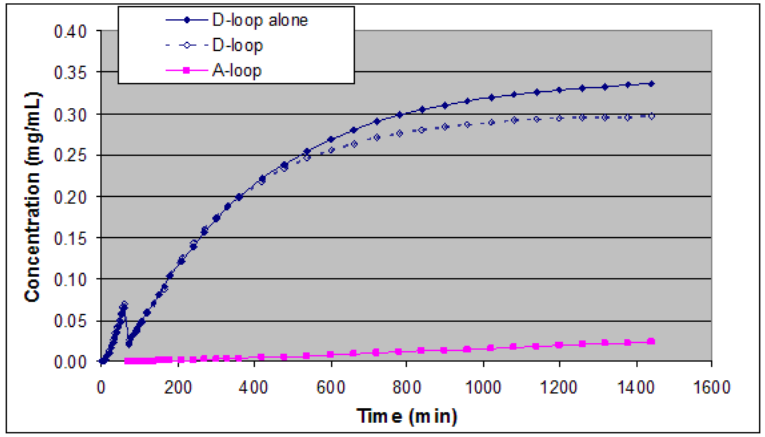
Fig. 7. Comparison of rescaled dissolution profile obtained from modified flow-through reservoir with *in vivo* data from reference (15)

Z Gao, *AAPS PharmSciTech*, 10(4), 2009, 1401-1405.

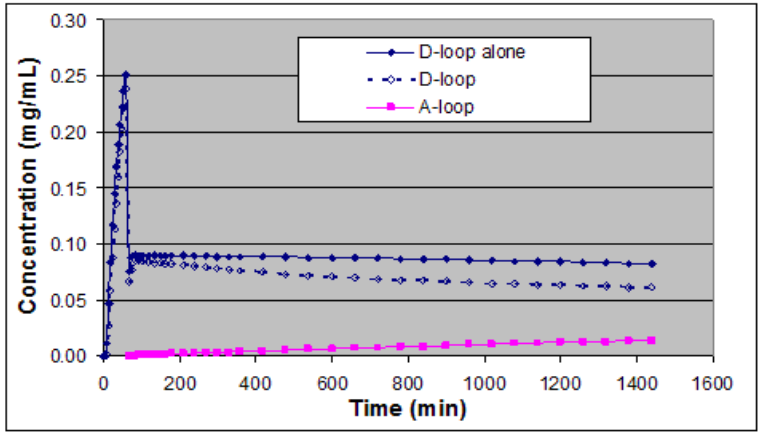
New Designs for Dissolution Testing



USP4 as dissolution apparatus @ 4mL/min
150 mL SGF for 1 hour
Then, 500 SIF for 23 hours



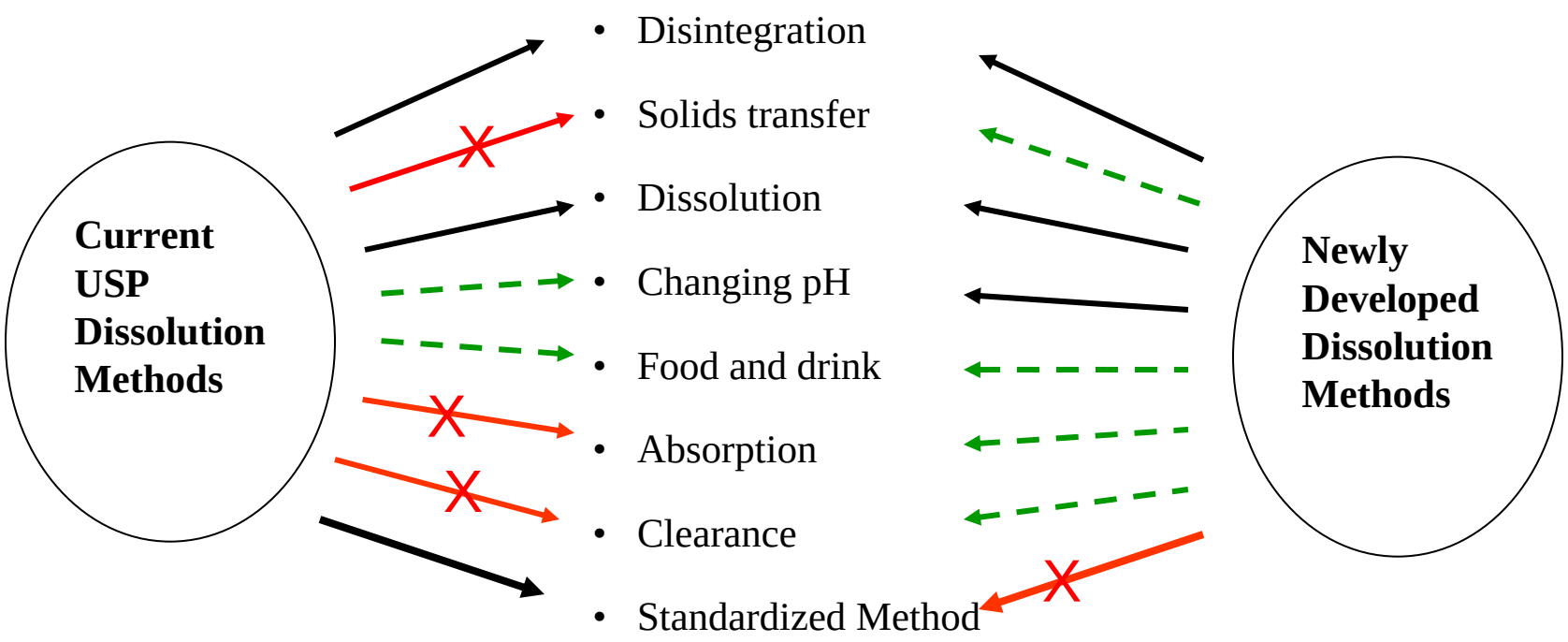
BCS I, propranolol HCl



BCS II, phenazopyridine HCl

Z Gao, *AAPS PharmSciTech*, submitted, 2012.

Advantage and Disadvantage of Newly Developed Dissolution Method



Dissolution Testing: Evolving Dissolution Media for Predicting *In Vivo* Performance

Arzu Selen, Ph.D.
Biopharmaceutics Research Lead
Office of New Drug Quality Assessment/OPS/CDER/FDA

Advisory Committee for Pharmaceutical Science
and Clinical Pharmacology
August 8, 2012

Outline

- Background
- Dissolution test to relevance of dissolution medium
  - Recommendations from the guidance
  - Types and function
  - Some examples: product characterization, food effect, screen for alcohol dose-dumping
  - Next phase? Integration of Quality-by-Design (QbD) and Biopharmaceutics and mechanistic value
- Summary

Dissolution Rate Linked with Clinical Outcome

"IN A RECENT study of factors affecting the absorption rate and gastrointestinal irritant effect of aspirin (1) it was concluded that (a) absorption rates and incidence and severity of local irritation are interrelated, (b) both of these characteristics are a function of the dissolution rate of aspirin in its particular dosage form, and (c) there are significant differences in in vitro dissolution rates among different nationally distributed brands of aspirin tablets."

Gerhard Levy, "Comparison of Dissolution and Absorption Rates of Different Commercial Aspirin Tablets", J. Pharm. Sci. Vol. 5, 388-392, 1961

From the Beginning

2009

2006

1990's

1987

1950's and 1960's

"A dissolution method (and the acceptance criteria) should be defined to deliver desired performance of a product in the intended *in vivo* environment." (Ref. 2)

- **IVIVC is a future objective for ER formulations**
- **Dissolution testing for process control, stability, minor formulation changes and manufacturing site changes. (Ref. 1)**

Ref.1: Workshop co-sponsored by ASCPT/DIA/APS/FDA, 1987
Ref.2: From "Commentary on AAPS Workshop, May 2006, Arlington, VA" C.Tong, S.S. D'Souza, and T. Mirza, Pharm. Res. 24 (9), 1603-1607, 2007

Our Increasing Expectations in Drug Dissolution/Release Testing

- Provide basic criteria for drug release from the product
- For batch to batch consistency/quality (product specification)
- As potential surrogate for *in vivo* BE studies
- For linking the product and its *in vivo* performance (correlations or relationships: IVIVC or IVIVR)

Recommendations from Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997)

- An aqueous medium- pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP)
- To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 (without enzymes)
- The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified.
- To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed (also, recommended for testing of ER products).
- A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0.

Recommendations for Dissolution Medium (Continued)

- With gelatin capsule products– medium containing enzymes (pepsin with SGF and pancreatin with SIF) may be used to dissolve pellicles.
- Use of water alone as a dissolution medium is discouraged *(water source may affect test conditions such as pH and surface tension, and may change during the dissolution test - due to the influence of the active and inactive ingredients)*
- For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate is recommended (Shah 1989, 1995). The need for and the amount of the surfactant should be justified.

A Short List of Dissolution Media

Standard Compendial (in USP):

- Simulated Gastric Fluid (with and without pepsin)
- Simulated Intestinal Fluid (with and without pancreatin)
- Water
- Their modifications (media with surfactants)

Additional Media (including patented “Biorelevant” media)

- Fasted-State Simulated Gastric Fluid (FaSSGF)
- Fed-State Simulated Gastric Fluid (FeSSGF)
- Fasted State Simulated Intestinal Fluid (FaSSIF)
- Fed State Simulated Intestinal Fluid (FeSSIF)
- Blank Fasted and Fed *(GF) and* (IF)
- And others (such as Ensure® Plus for forecasting food-effect)

Composition of FaSSGF and FeSSGF

Fasted State Simulated Gastric Fluid (FaSSGF), pH 1.6 [30]

Composition

Bile salt (sodium taurocholate)	80	µM
Lecithin	20	µM
Pepsin	0.1	mg/mL
Sodium chloride	34.2	mM
Hydrochloric acid qs	pH 1.6	
Deionized water qs ad	1	L

Fed State Simulated Gastric Fluid (FeSSGF), pH 5.0 [31]; blank medium

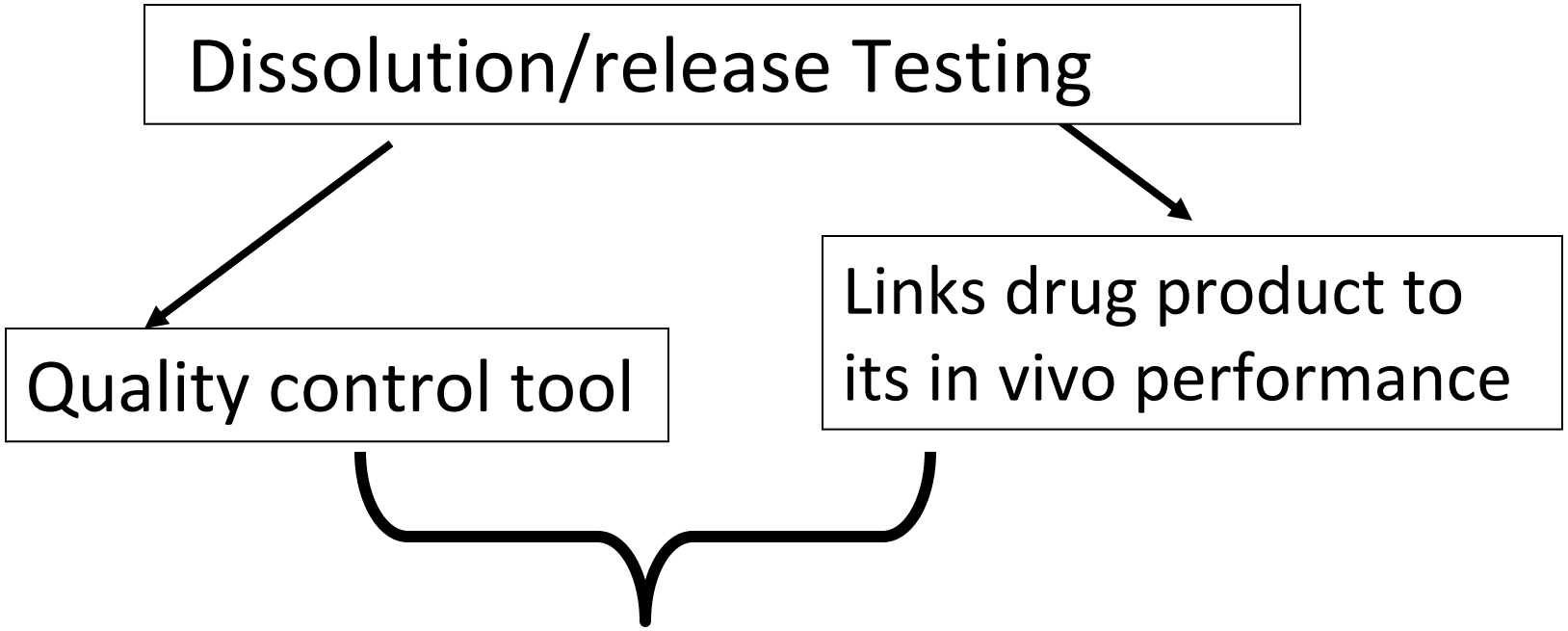
Composition

Glacial acetic acid	17.12	mM
Sodium acetate	29.75	mM
Sodium chloride	237.02	mM
Deionized water qs ad	1	L

The blank medium was then mixed with UHT-milk at the ratio of 1:1

Reference: Jantratid et al., Europ. J of Pharm. and Biopharm. 69, 776-785, 2008

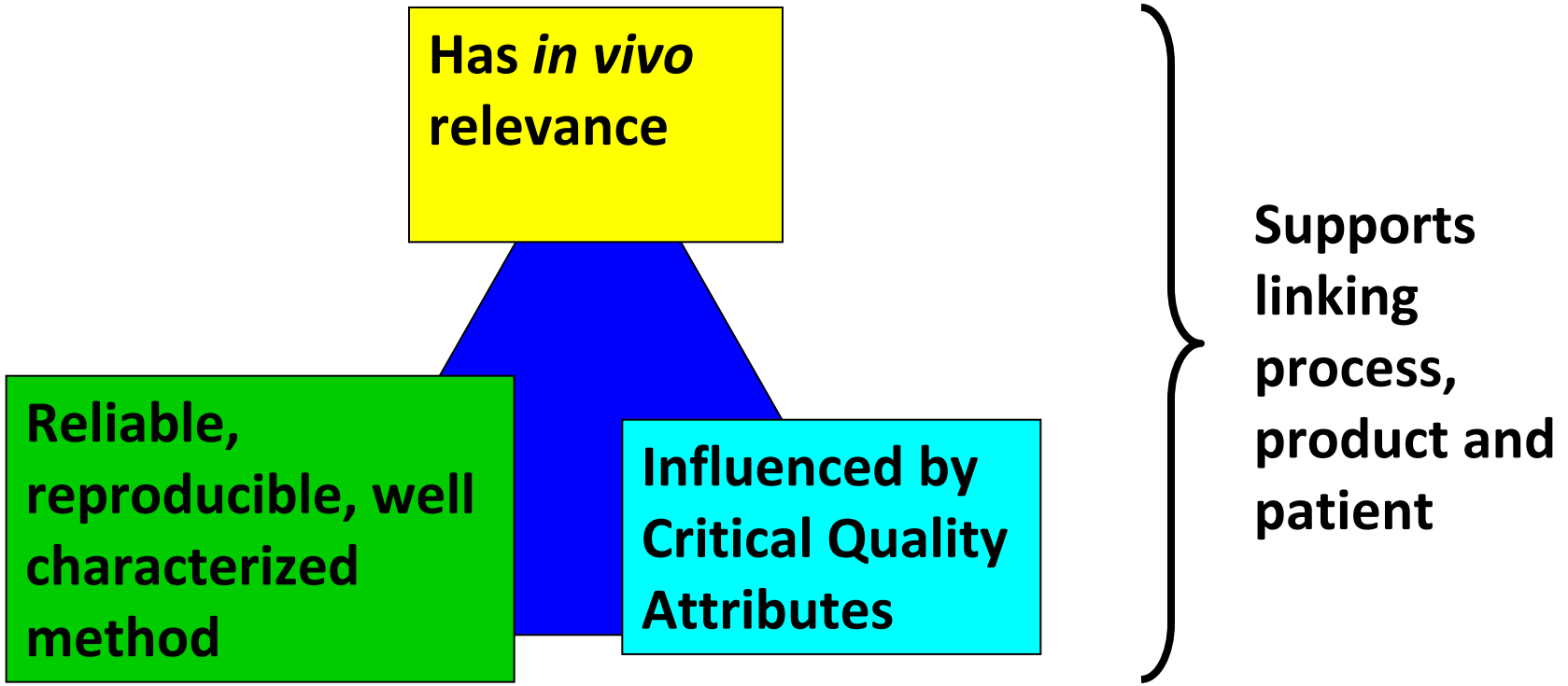
Last 20 - 30 years:



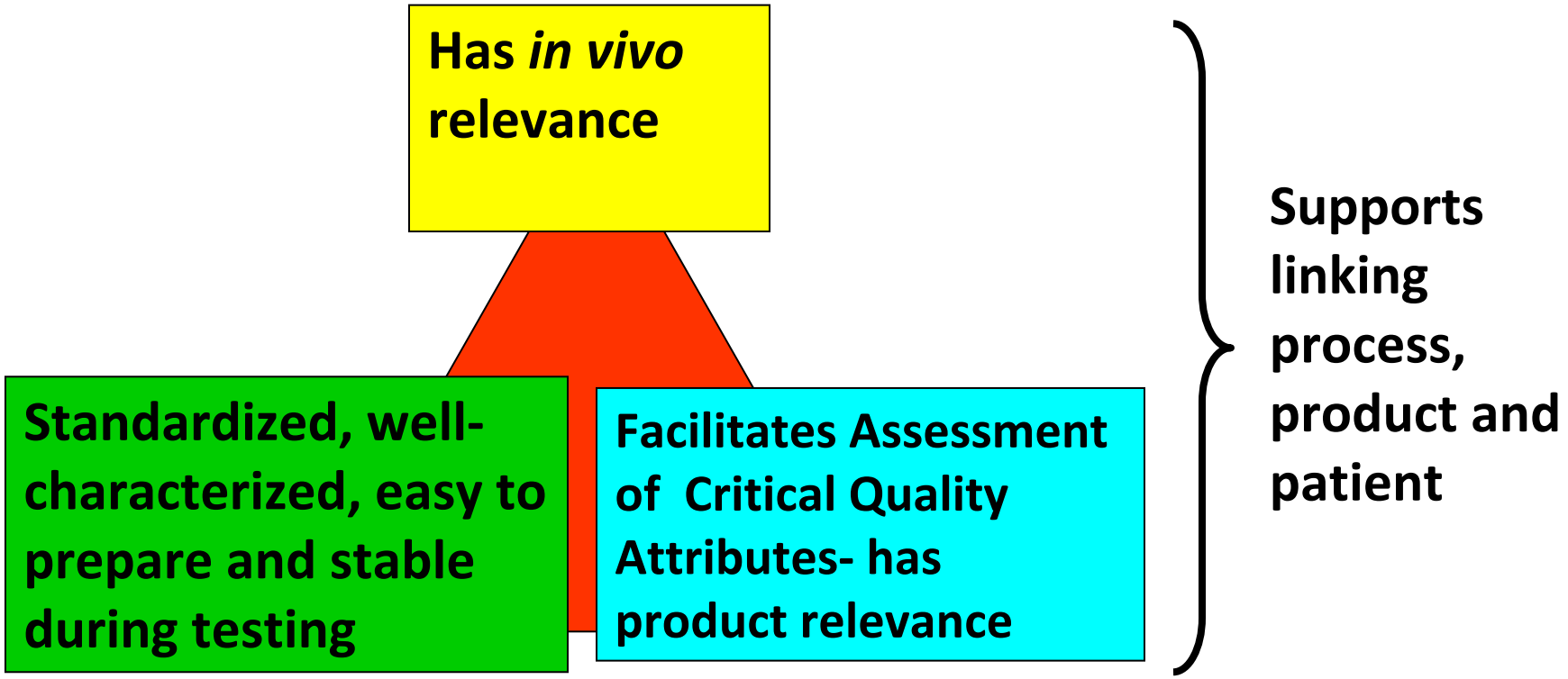
And recently:

- **Can/should QbD merge the two paths?**
- **Does it help if single and/or multiple media are used?**

Desired State for Drug Release/Dissolution Method



Desired State for Drug Release/Dissolution Media



Considerations for Selection of Dissolution Medium

- Consistent with route of drug administration and *in vivo* environment (Relevance)
- Physiological and conditional similarity (such as fed/fasted)
- Function (mechanistic understanding, exploratory vs. predictive)
- Possible alternates (such as simplified media)
- Ease of preparation (reliable method)
- Standardized (reproducible and stable during testing)

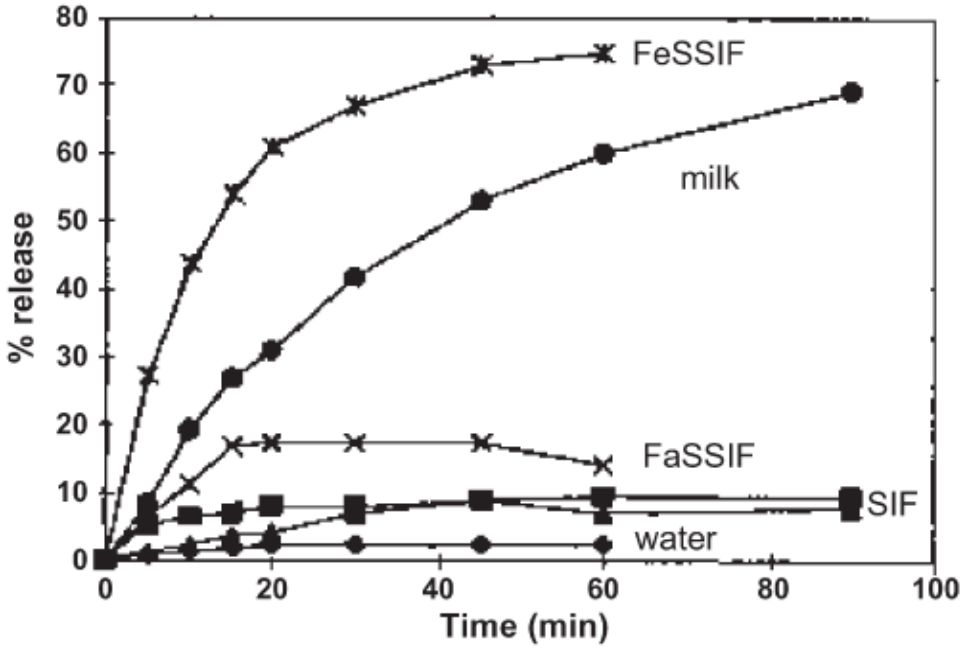
In Vitro Tests for Product Characterization

(using compendial and/or non-compendial methods)

- USP Apparatus and compendial media (and/or modifications)
  - ❖ Assessing solubility, dispersion and conditions leading to precipitation
- Bile salt solubility
  - ❖ Exploring *in vivo* solubilizing capacity of gut lumen
- Formulation dispersion, dissolution and drug precipitation
  - ❖ Formulation development
  - ❖ Testing changes in formulation and product and environment interactions (food-effect, alcohol dose-dumping)
- *In vitro* digestion/lipolysis tests as possible predictors for food effect (effect of the digestion products)

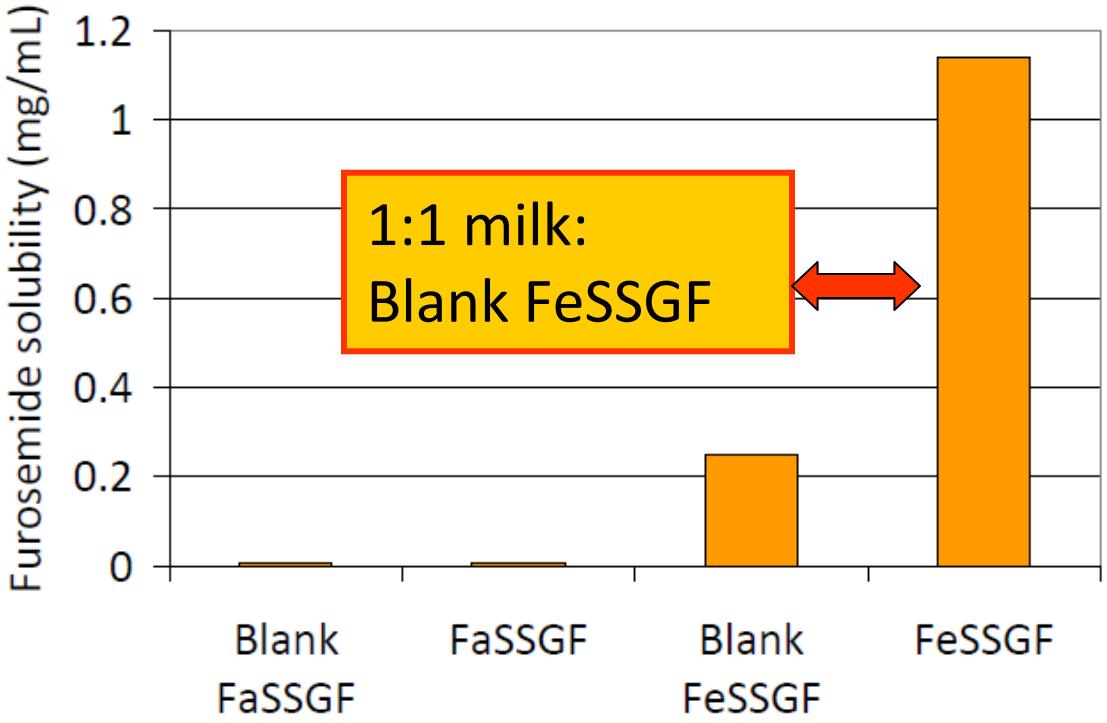
Effect of Likely Components in the Gut Lumen on Rate and Extent of Dissolution

Mean Dissolution Profiles of Romazin Tablets (Troglitazone®) in Various Media



References: Nicolaides, Galia, Efthymiopoulos, Dressman, and Reppas. Pharm. Res. 16: 1877–1883, 1999 and C.W. Pouton, Europ. J. of Pharm. Sci. 29, 278-287, 2006

Furosemide Solubility in Simulated Gastric Media

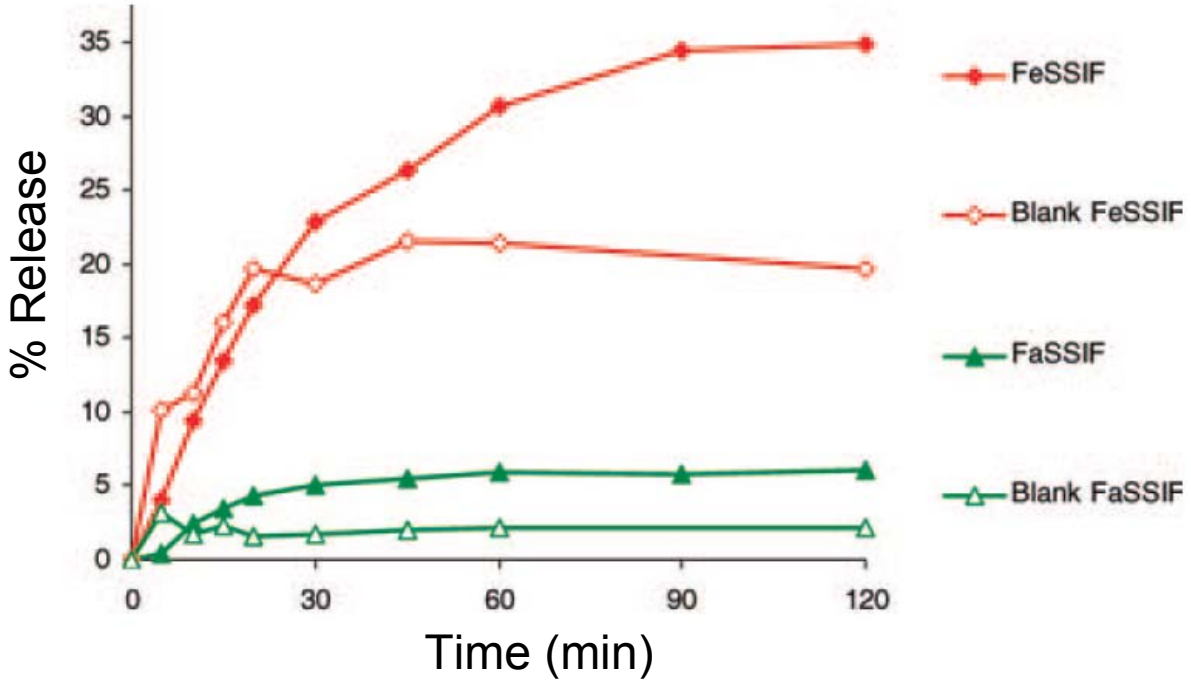


FaSSGF (Fasted-State Simulated Gastric Fluid, pH 1.6) and FeSSGF (Fed State Simulated Gastric Fluid, pH 5), and corresponding blank buffers (without surfactant)

Reference: From the 2011 AAPS poster presentation of Sarah Gordon, Anette Muellertz and others

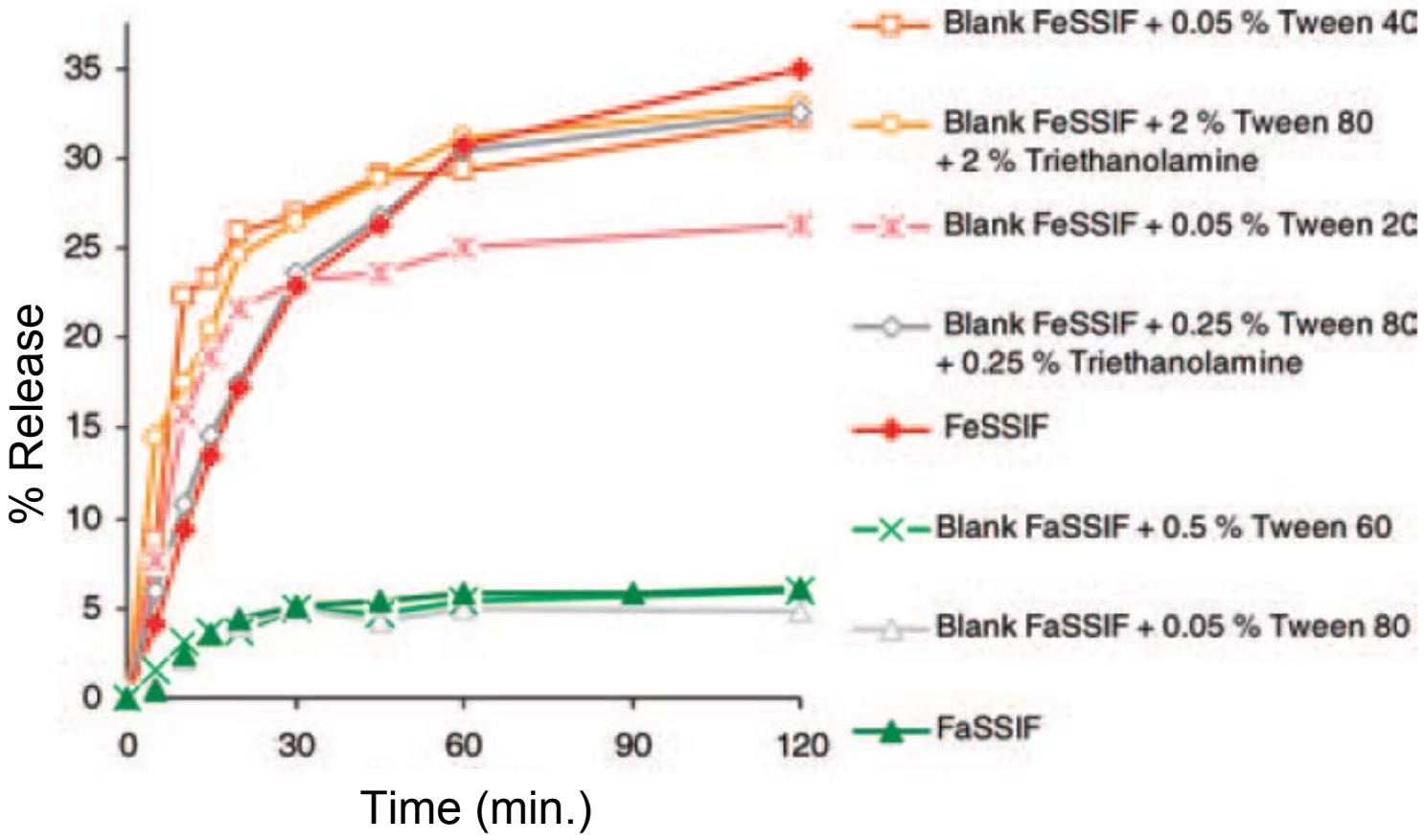
Exploring Food Effect and Possible Use of Simplified Biorelevant Media

Ketoconazole Release from Nizoral® Tablets in Biorelevant Media and Respective Blank Buffers



Reference: T. Zoeller and S. Klein, Dissol. Technol. 8-13, November 2007

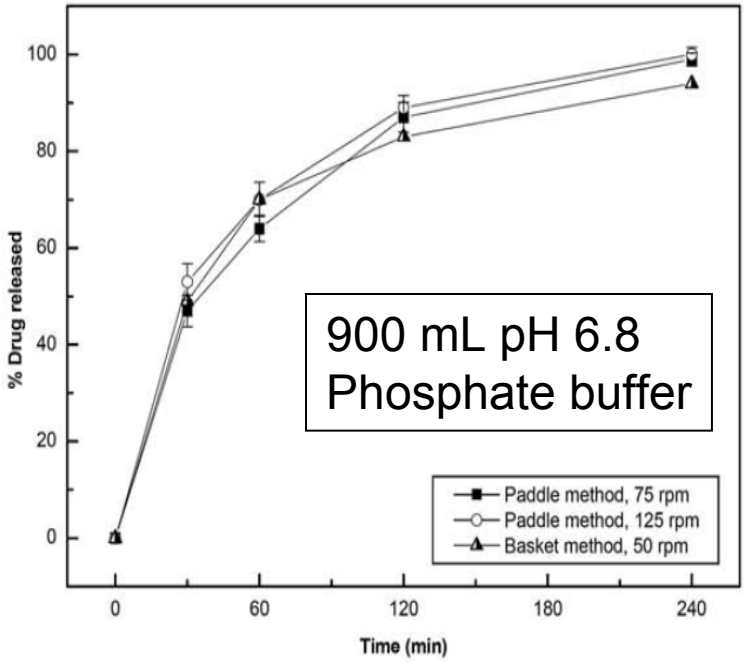
Ketoconazole Release from Nizoral® Tablets in Simplified "Biorelevant" Dissolution Media (Continued)



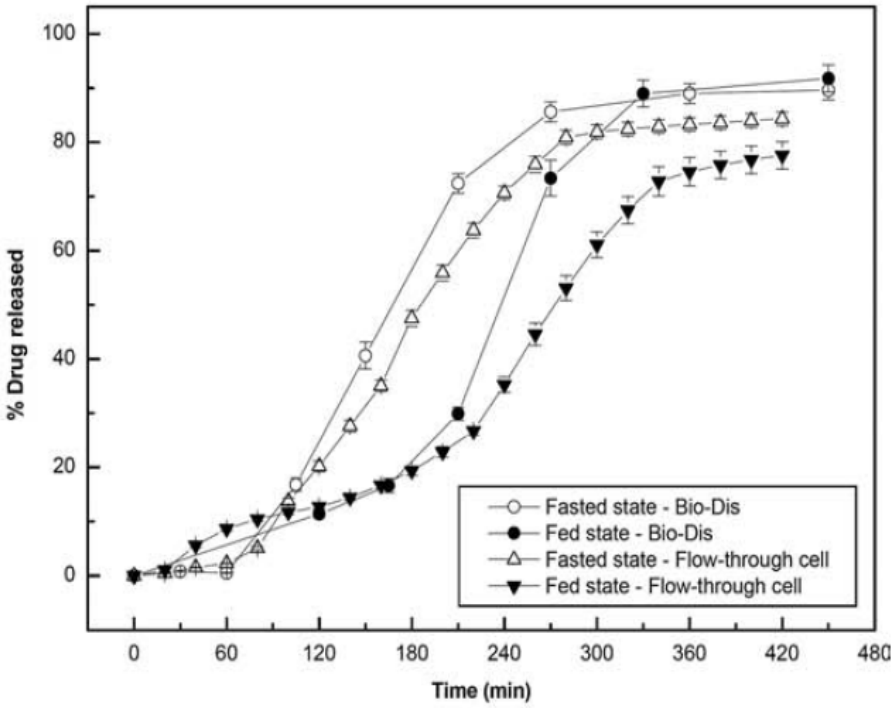
Single Medium vs. pH Gradient Method

Diclofenac release from diclofenac sodium modified release pellets
(E. Jantratid, V. De Maio. E. Ronda et al. Eur. J. Pharm. Sci. 37, 434-441, 2009)

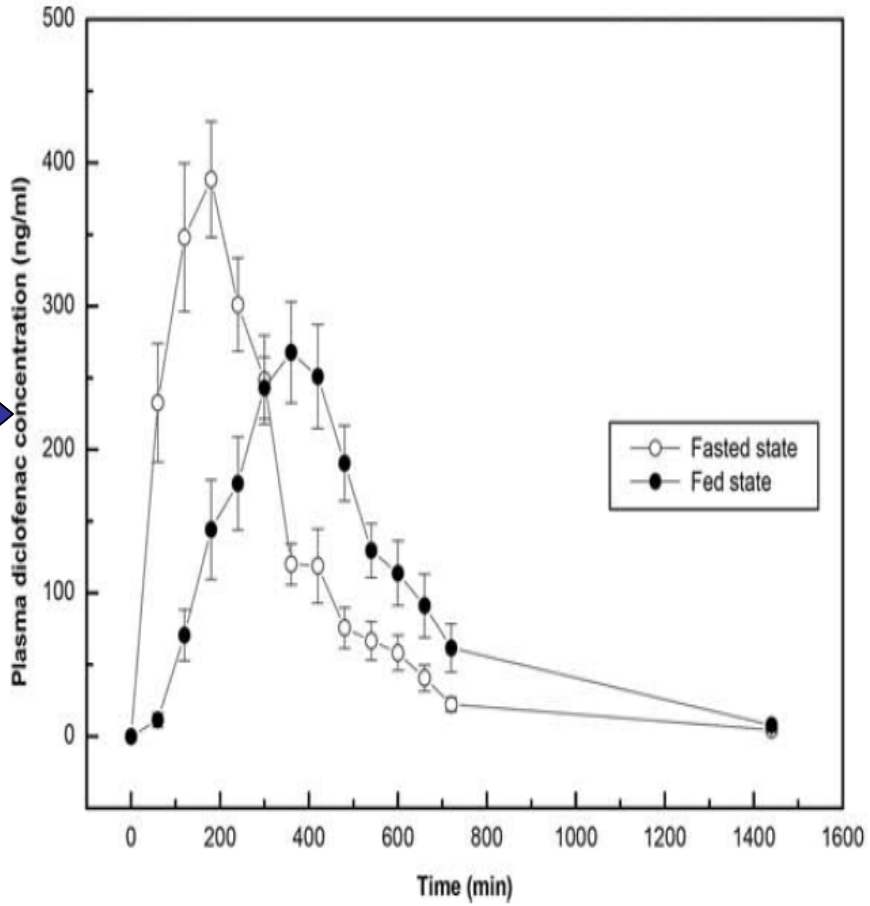
Single Medium



Biorelevant pH Gradient Method

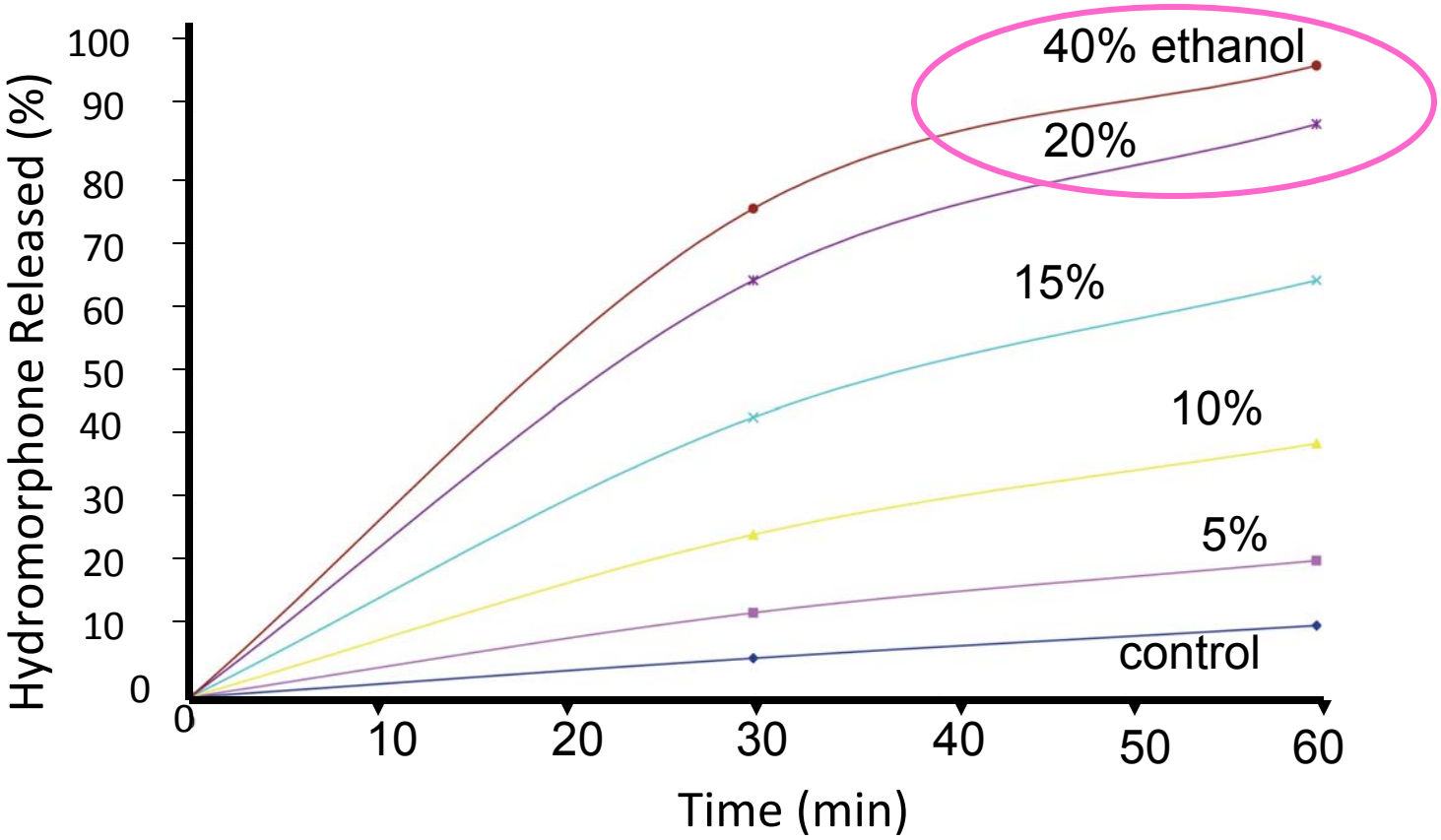


In vitro results from the biorelevant pH gradient method predict food effect



Plasma diclofenac concentrations after a single oral dose of modified-release diclofenac sodium pellets (n=16 healthy volunteers, fasted and fed states).

In Vitro Release of Opioids from Oral Prolonged-release Preparations in Simulated Gastric Fluid and Simulated Gastric Fluid with Ethanol

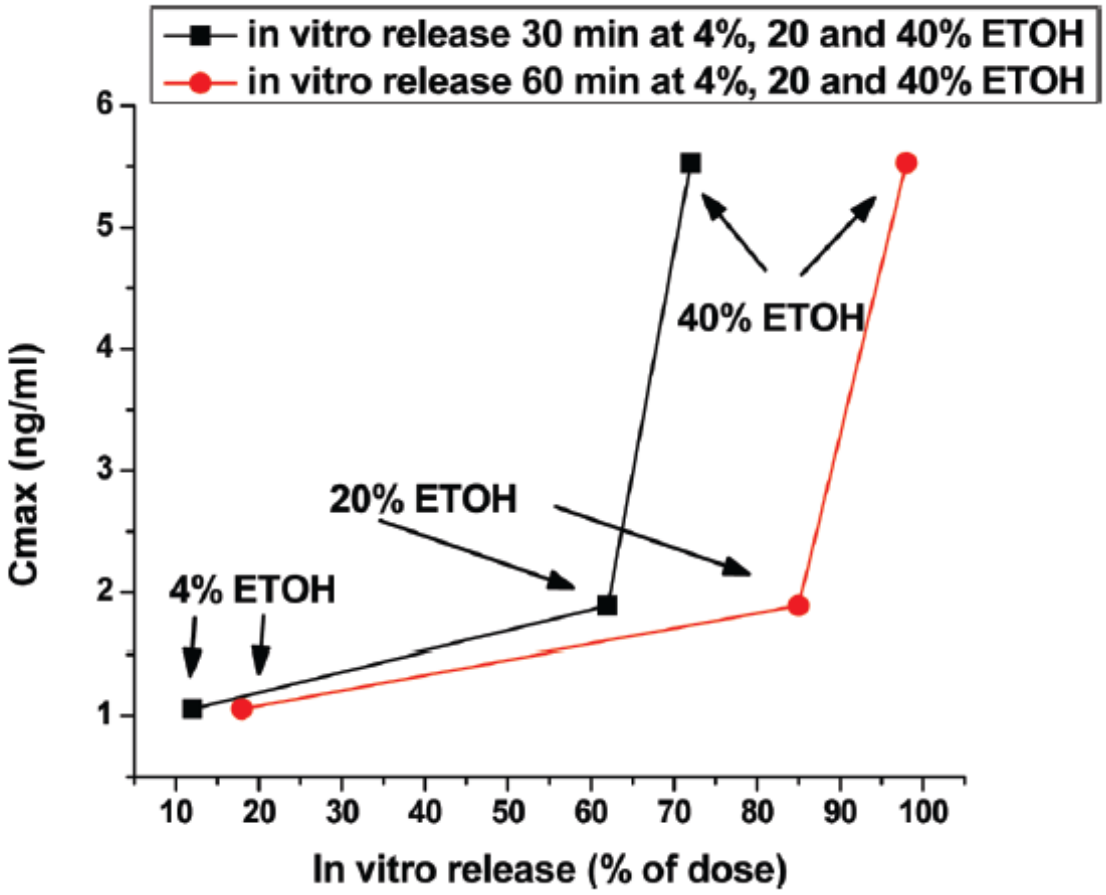


Reference: Walden et al, D*rug Dev. And Indust. Pharm.* 33:1101–1111, 2007

Screening for Alcohol Effect on Drug-Product Integrity

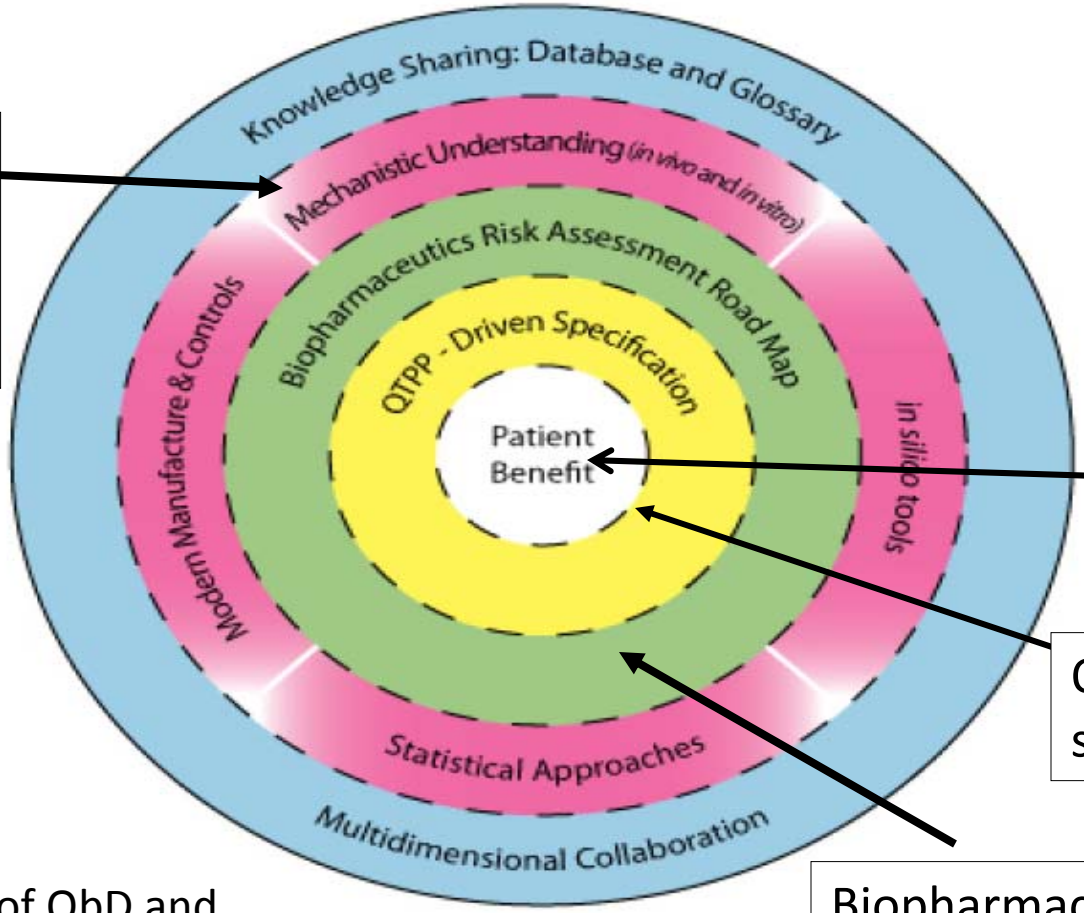
Correlation Between Hydromorphone Cmax and *In Vitro* Release at 30 min and 60 min

Palladone XL was given with 240 mL water and also with 4%, 20% and 40% alcoholic beverage



Reference: Lennernas,Molec. Pharma. 6(5), 1429-1440, 2009

Integration of QbD and Biopharmaceutics



Mechanistic Understanding (*in vivo* and *in vitro*)

Patient Benefit

QTPP driven specification

Biopharmaceutics Risk Assessment Road Map

June 2009 workshop of QbD and Biopharmaceutics Rockville, MD
Ref.: AAPSJ, 12(3), 465-472, September 2010

Summary: Towards Developing an *In Vitro* Test Mimicking *In Vivo* Conditions (Mechanistic/Predictive Methods)

- Dissolution/release test method should be well characterized (sources of variability and the impact of changes should be known).
- Dissolution test media should be physiologically meaningful.
- Dissolution/release test conditions (e.g. agitation), duration and sample collection times should be consistent with its intended release pattern/environment, and use (as in Quality Target Product Profile).

Oral Bioperformance
&
21st Century Dissolution Testing

Gregory E. Amidon
Research Professor of Pharmaceutical Sciences
College of Pharmacy
University of Michigan

“What is it that we can’t do today, but if we could, it would revolutionize our business?”

Joel Barker

Futurist

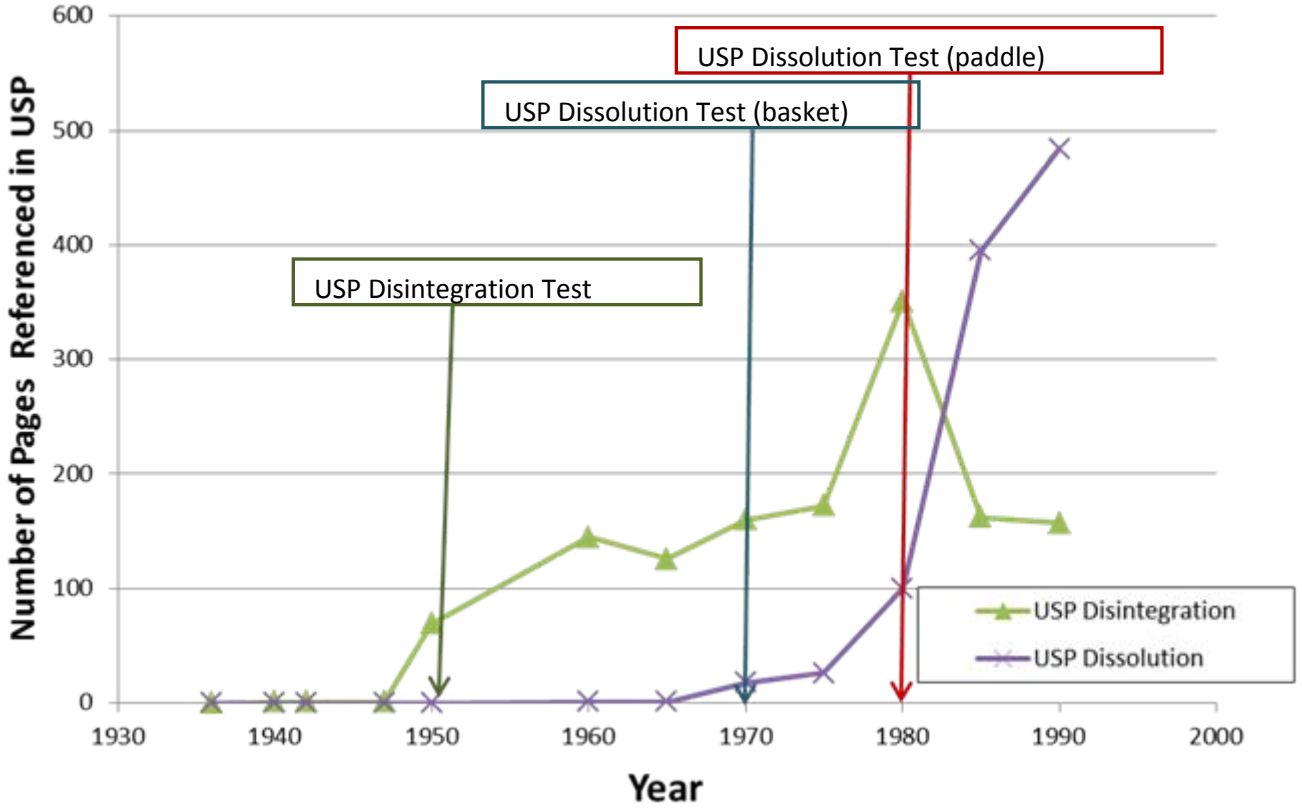
Comprehensive computational tools and meaningful in vitro test methods that accurately reflect and predict oral bioperformance would revolutionize oral formulation development.

Topics

- Where are we now?
- What opportunities are there? There are many!
  - GI physiology
    - Fluid volume
    - Hydrodynamics
    - Buffer (bicarbonate)
  - Advanced dissolution methods
    - Two phase systems (simulating dissolution and absorption)
    - Two compartment systems (simulating stomach and intestine)
  - Computational Tools
    - Fluid Dynamics
    - Dissolution
    - Absorption Modeling

USP Compendial Tests for Oral Bioperformance

- 1950: Disintegration Test
- 1970: Dissolution Apparatus 1 (rotating basket)
- 1980: Dissolution Apparatus 2 (paddle)
- …….
- …….



Dissolution Testing is what links the dosage form to the proven efficacy (eg: typically the clinical lot used in the Phase 3 pivotal efficacy study)!

.....

Dissolution testing is what links every lot of the dosage form from every manufacturer to the labeling (proven efficacy and safety)! This can be 100s or 1000s of lots separated by years or decades as well as continents from the pivotal efficacy lot.

Some areas of success (1970-2012)

- Dissolution Testing as an “analytical” measure of:
  - Product consistency
  - Product quality
  - Manufacturing process control
- IVIVC, IVIVR, IVIVE
- BCS
- Intestinal media simulation
  - FaSSIF
  - FeSSIF
- Physiologically relevant solubility
- Improved understanding of GI environment
- Application of computational tools

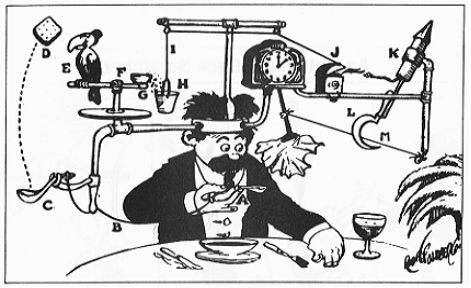
Some weaknesses (1970-2012)

- IVIVC, IVIVR, IVIVE
- Application of oral physiology understanding to drug and drug product testing
- Dissolution Testing as in vivo simulation
- Application of advanced computational tools
- Application of comprehensive physicochemical principles to oral absorption

The price of “less than ideal” in vitro methods is:

- Over-discriminatory in vitro test methods
  - Result is wasted resources and delays in the development of new products to meet unmet medical needs
    - Chasing down unimportant problems
    - Conducting unnecessary clinical or animal testing
    - Spending unnecessary development and analytical resources
    - Slowing development of innovative dosage forms for difficult to deliver drugs
- Under-discriminatory in vitro test methods
  - Result in a lack of meaningful product quality control
    - Difficulty comparing innovator and generic products
    - Product failure (eg: efficacy and/or safety) in patients!

A better dissolution test!



Rube Goldberg

*More Accurate Oral Biop*erformance Prediction would help:

- Formulation finding/screening (early development)
- Define meaningful in vitro performance requirements such as disintegration, dissolution, supersaturation extent and time, functional excipient impact (solubilizer, precipitation inhibitor) etc.
- Optimize dosage form delivery rate
- Enhance material and process understanding (≡ Quality by Design)
- Facilitate meaningful in vitro testing of varying in vivo conditions

Topics

- Where are we now?
- What opportunities are there (there are many)?
  - GI physiology
    - Fluid volume
    - Hydrodynamics
    - Buffer (bicarbonate)
  - Advanced dissolution methods
    - Two phase systems (simulating dissolution and absorption)
    - Two compartment systems (simulating stomach and intestine)
  - BCS Advances
  - Computational Tools
    - Fluid Dynamics
    - Dissolution
    - Absorption Modeling

What have we learned about human physiology that might related to dissolution testing?

Key considerations include:

- Fluid volume
- Intestinal surface area
- Buffer (bicarbonate)
- pH (average, range)
- Ionic strength
- Surfactants (bile acids)
- Carbonic anhydrase
- Hydrodynamics
- Residence time
- Stomach emptying rate
- ….

Intestinal Contents

Bicarbonate (mEq L^{-1}) ←
Bile salts (mM)
Lipids (mg/mL)
Phospholipids (mM)
Pepsin (mg/mL)
Lipase
Potassium (mM)
Sodium (mM)
Chloride (mM)
Calcium (mM)
Buffer capacity (mmol L^{-1} pH^{-1}) ←
Osmolality (mOsm kg^{-1})
Surface tension (mN m^{-1})
Viscosity
Volume ←
Shear ←
pH ←

Physiology: What volume of liquid is the dosage form exposed to?

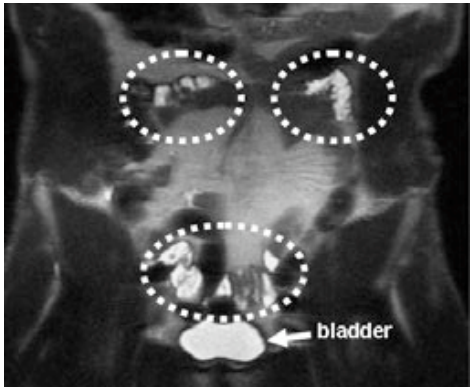
- Average aqueous volume in the fasted small intestine is ~100 ml (Refs: multiple)

	Total volume in the small intestine	
Fasted	Mean	86, 81, 112±27, 109 ± 36, 165±22, 105±72
	Range	34-46, 37-130, 45-319
Fed	Mean	47, 381, 590±73, 54±41
	Range	18-78, 343-491, 20-156

~ 100 mL

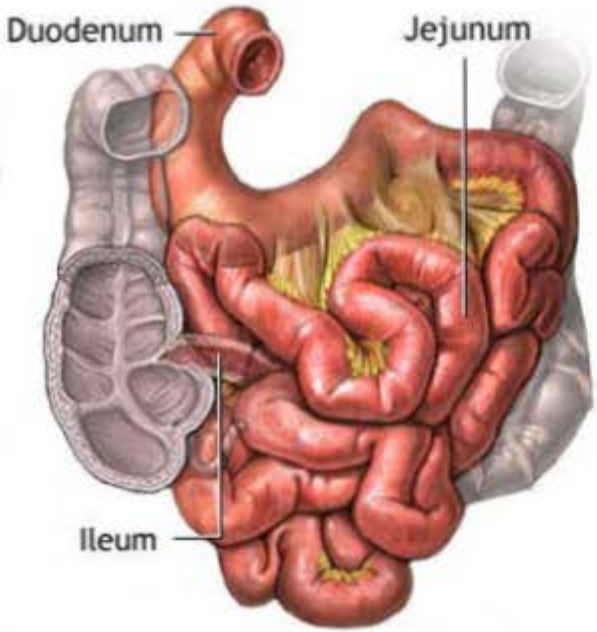
- Evidence of liquid pockets Schiller et al. *Aliment Pharmacol .Ther. 22:971-979 (2005).*

		Fasted	Fed
Number of liquid pockets	Mean	4	6
	Individual (approx.)	2, 3, 4, 5, 8	2, 5, 6, 7, 11
Volume of liquid pocket (mL)	Median	12	4



Ref: D.M. Mudie, G.L. Amidon, and G.E. Amidon. Physiological Parameters for Oral Delivery and In Vitro Testing. Mol Pharmaceutics. *7:1388-1405 (2010).*

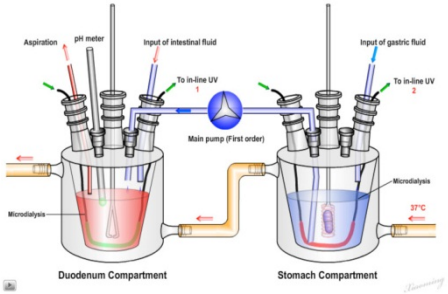
Physiology is complex



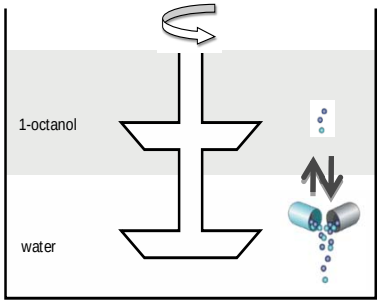
So - compendial dissolution testing in 900 mL with a paddle (or rotating basket) doesn't really capture it.

Some physiological dissolution “systems”

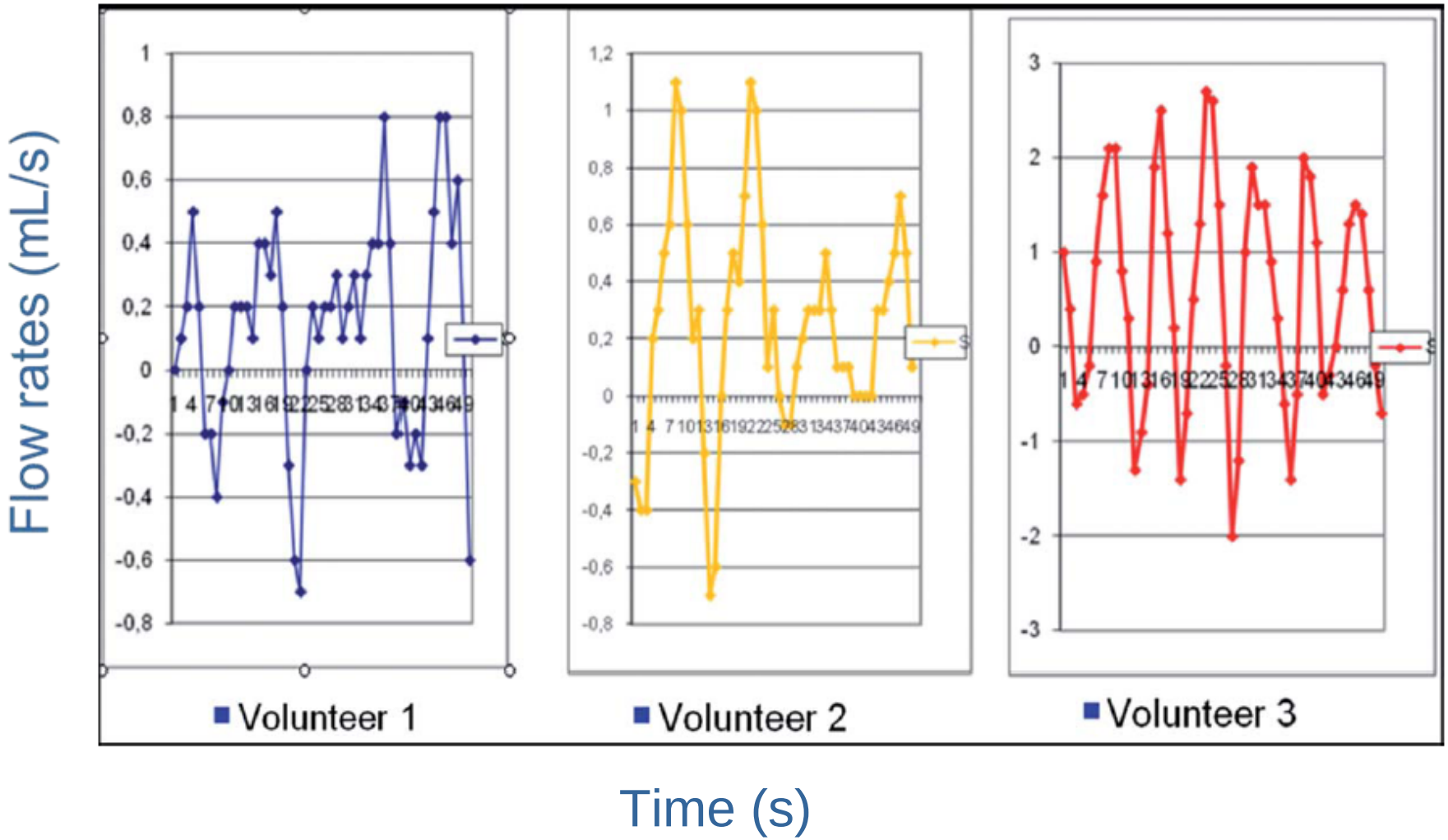
- Artificial Dynamic GI System, TIM-1 (TNO)
- Stress test apparatus
- Dissolution/Permeation system (uses Caco-2 cells)
- Two-compartment apparatus:
  - Artificial Stomach and Duodenum (ASD)
  - FloVitro Technology (Rohm and Haas)



- Two-phase dissolution apparatus
  - Simultaneous dissolution and partitioning in single compartment containing two phases (water:organic)



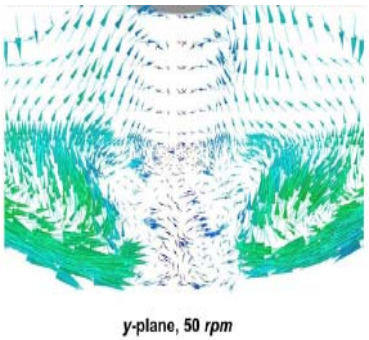
In-vivo Intestinal Fluid Flow Rates

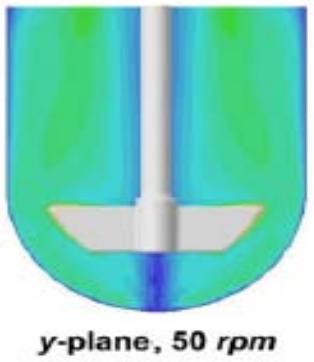


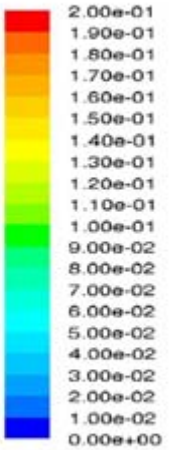
Gutzeit A, Patak MA, Weymarn Cv, Graf N, Doert A, Willemse E, Binkert CA, Froehlich JM 2010. Feasibility of Small Bowel Flow Rate Measurement With MRI. Journal of Magnetic Resonance Imaging 32:345-351.

Hydrodynamics of dissolution apparatus: USP Apparatus 2 - Velocity & Shear Profiles

- Highest velocities occur at the tip of the paddle (~20 cm/sec)
- The lowest velocities are directly beneath the centerline of the impeller and around the shaft of the impeller.



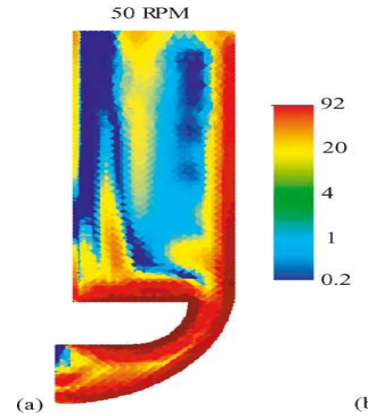




- The Reynold's numbers (Re) vary depending on the rotational speed and location(Re ~ 10^4).
- The shear rates throughout the vessel are heterogeneous.

  Maximum shear rates: $92s^{-1}$ at 50 RPM

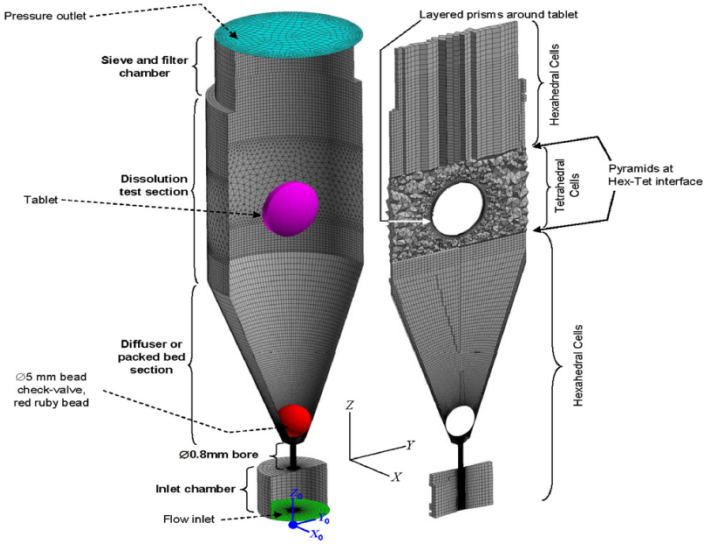
  Average shear rates: ~ $20s^{-1}$ at 50 RPM



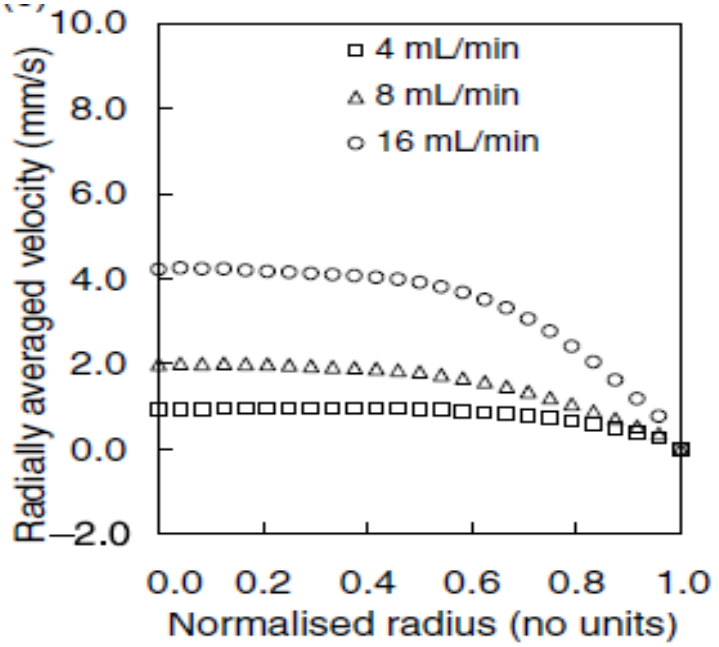
Ref: Bai G, Wang Y, Armenante PM 2011. Velocity Profiles and Shear Strain Rate Variability in the USP Dissolution Testing Apparatus 2 at Different Impeller Agitation Speeds. International Journal of Pharmaceutics 403:1-14.

Flow Through Cell

- May allow for testing at more physiologically relevant Reynolds number (5 – 300) and flow rates (0.1 – 0.6 cm/sec).

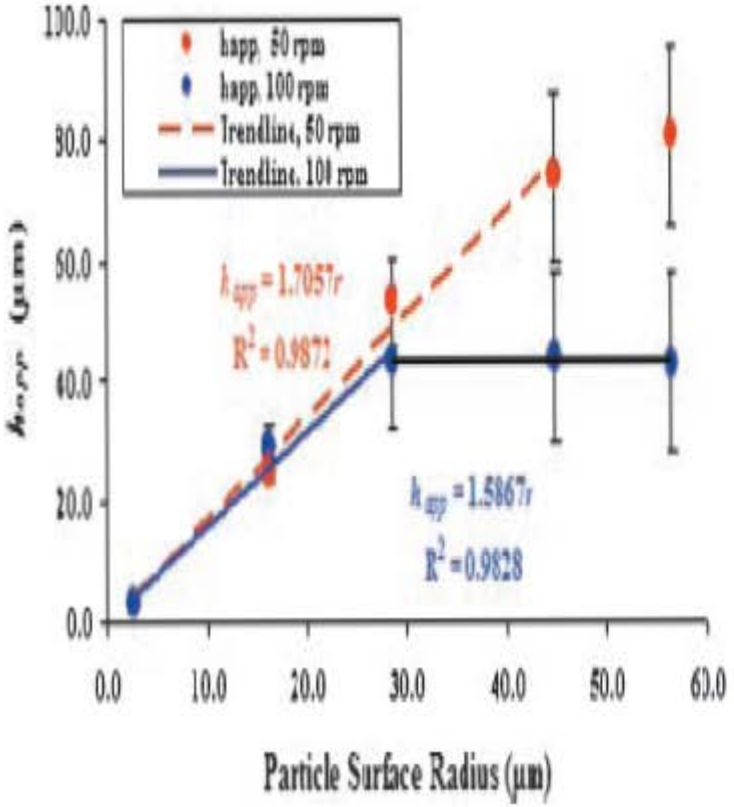


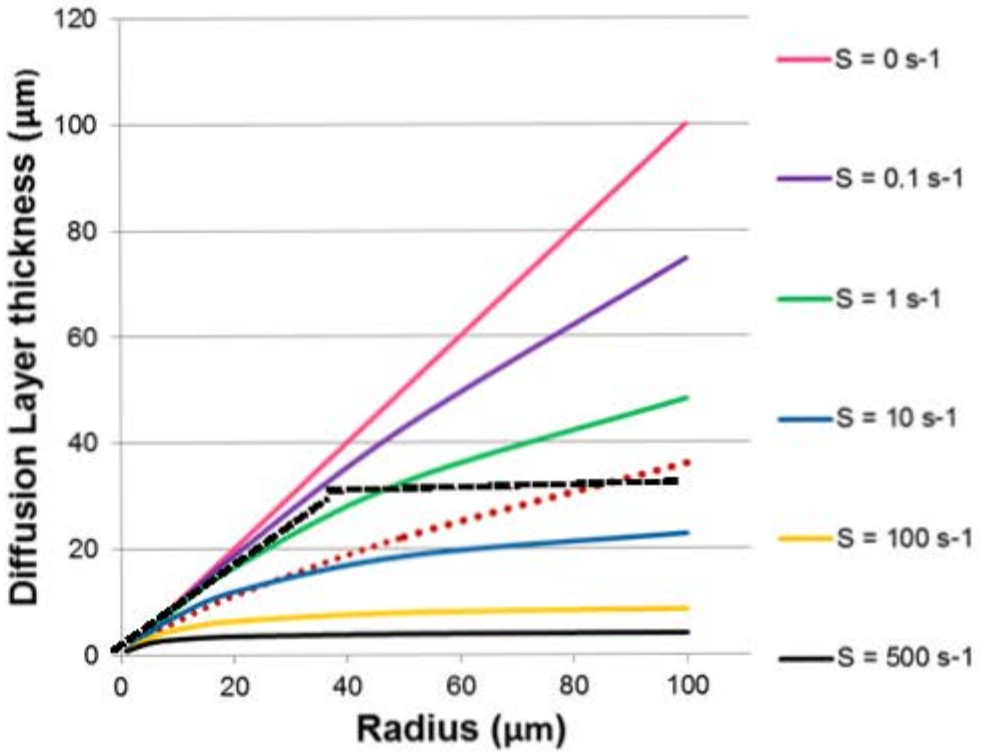
Velocity Profiles in a 12mm Cell



Ref: Schematic of a flow through cell: Kakhi (2009). Mathematical Modeling of the Fluid Dynamics in the Flow Through Cell. International Journal of Pharmaceutics. *Vol 376, pg 25.*

Impact of Fluid Shear on Particle Dissolution (h_{app}): High Performance Computational Analysis





Hintz, Johnson (1989)

Predicted based on human intestinal shear rates

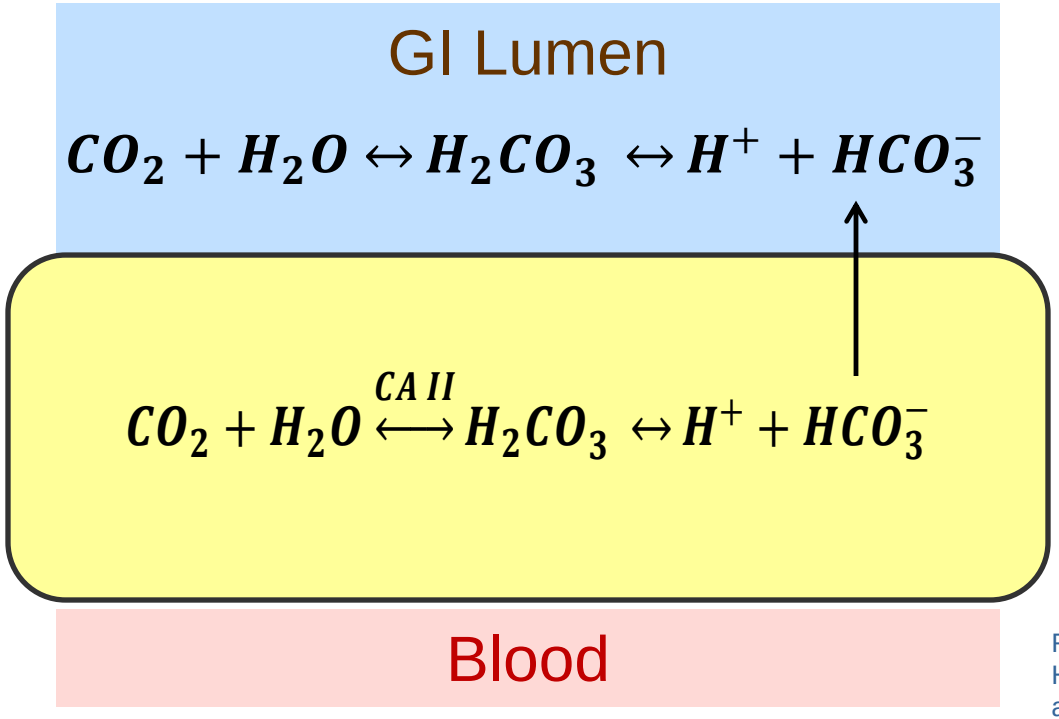
Ref: (1) JJSheng, etal. JPharmSci. 97:4815-4829 (2008).
(2) Wang, Brasseur, Penn State University (unpublished)

Importance of physical chemistry and physiologic buffer (bicarbonate)

- Drug Properties:
  - Solubility
  - pKa
  - Diffusion coefficient
  - Particle size
- Physiological Properties:
  - pH
  - Buffer species and concentration
  - Fluid hydrodynamics
  - Intestinal motility
  - Bulk concentration
  - Volume and temperature etc.

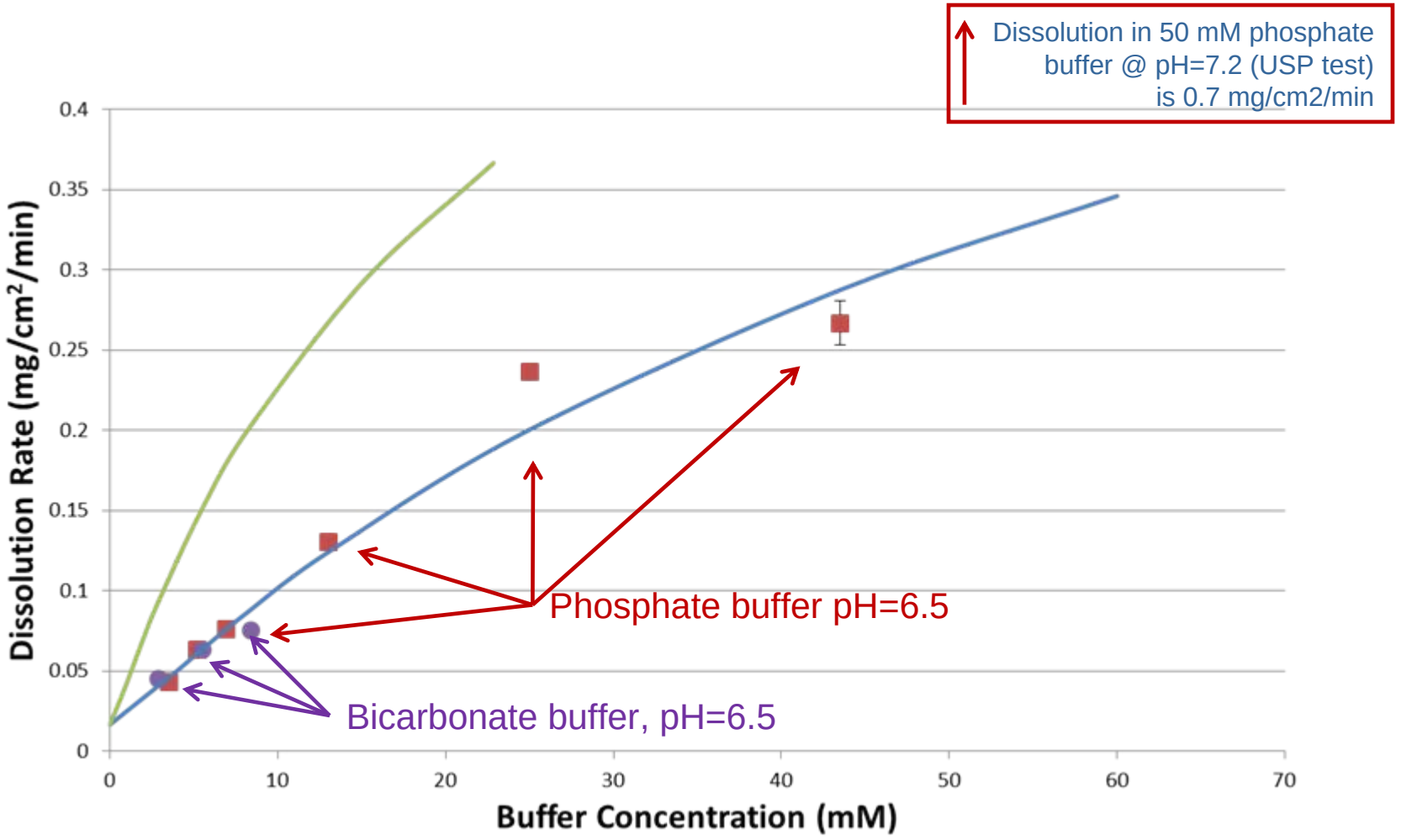
Bicarbonate Buffer Physiological Relevance

- Bicarbonate is secreted by the pancreas and epithelial cells throughout the GI lumen.



Ref: Sly WS, Hu PY 1995. Human Carbonic Anhydrases and Carbonic Anhydrase Deficiencies. Annu Rev Biochem 64:375 - 401

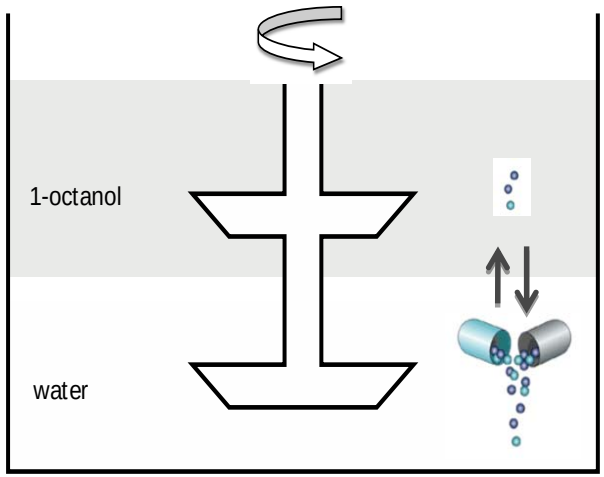
Dissolution (37°C) of Ibuprofen in bicarbonate buffer compared to phosphate buffer (rotating disk)



Topics

- Where are we now?
- What opportunities are there (there are many)?
  - GI physiology
    - Fluid volume
    - Hydrodynamics
    - Buffer (bicarbonate)
  - Advanced dissolution methods
    - Two phase systems (simulating dissolution and absorption)
    - Two compartment systems (simulating stomach and intestine)
  - BCS Advances
  - Computational Tools
    - Fluid Dynamics
    - Dissolution
    - Absorption Modeling

Combining dissolution and absorption (two phase model)

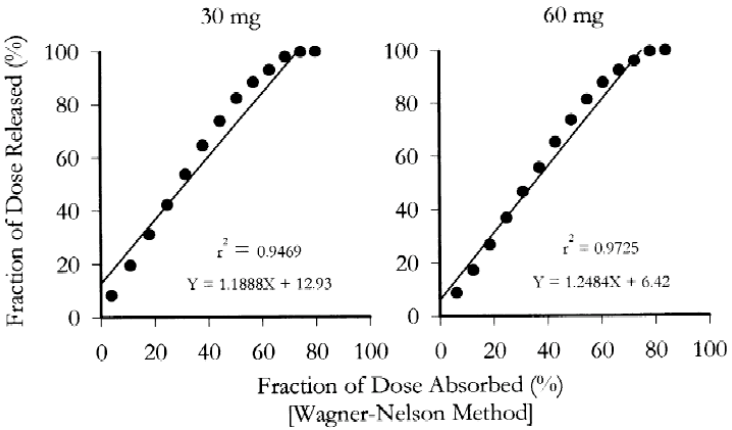


- Ten + systems described in literature
- Being used in industry
- Overcome difficulties in maintaining sink conditions for poorly-soluble drugs (BCS 2, 4), super-saturable systems, and controlled-release
- Circumvent analytical difficulties associated with lipid-based capsule formulations
- Simultaneously study impact of formulation changes (e.g. surfactants) on dissolution and absorption processes!
- Can potentially be scaled to more accurately reflect in vivo conditions!

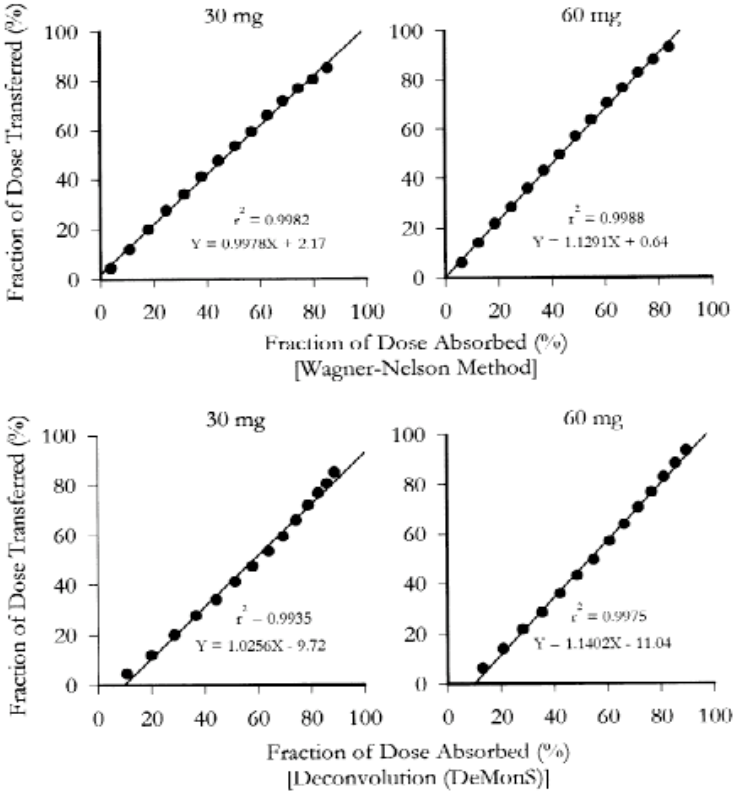
Two-phase IVIVR: Nifedipine GITS tablets

- BCS IIc
- Sol. FaSSIF = 0.024mg/ml
- Log P = 2 - 4

Single-phase

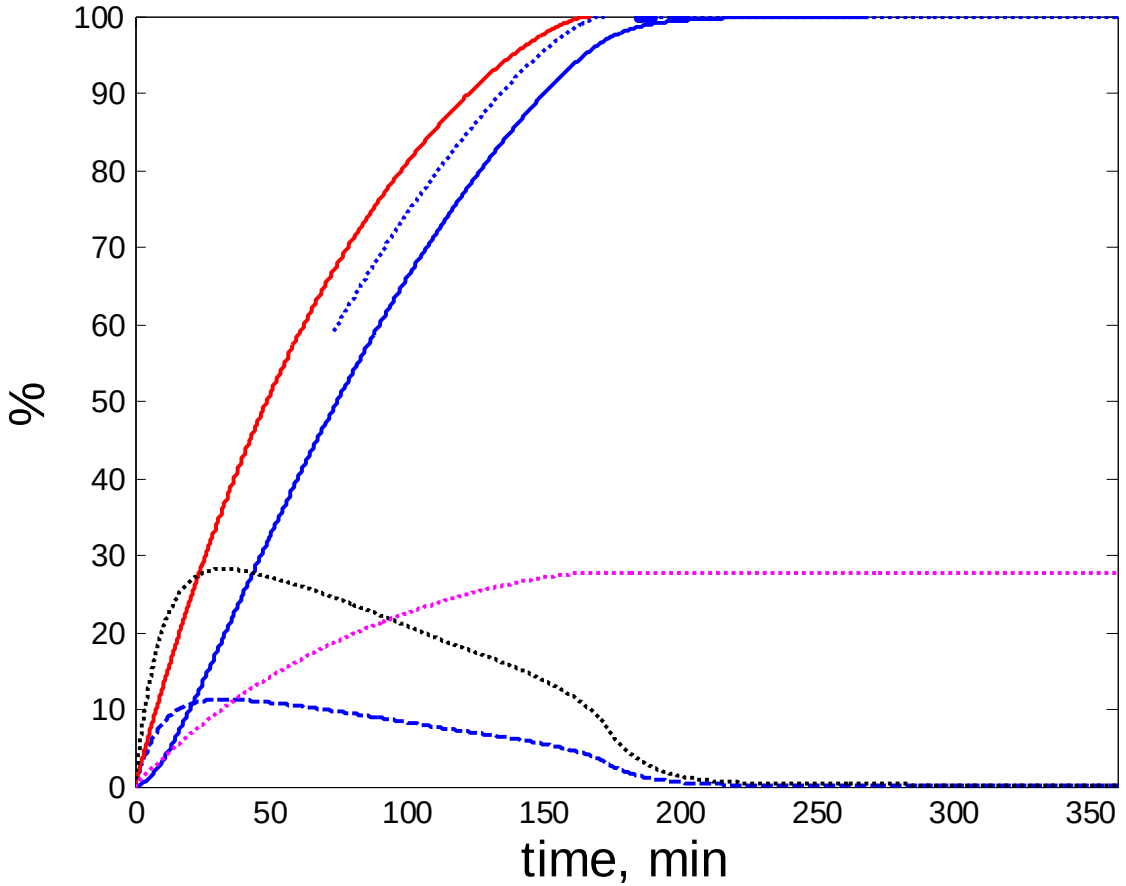


Two-phase



Two phase physiologic dissolution model

P_m= 5 x 10^{-4} cm/sec, particle radius = 50 µm



BCS Class II

Sol=100µg/mL Dose = 25 mg

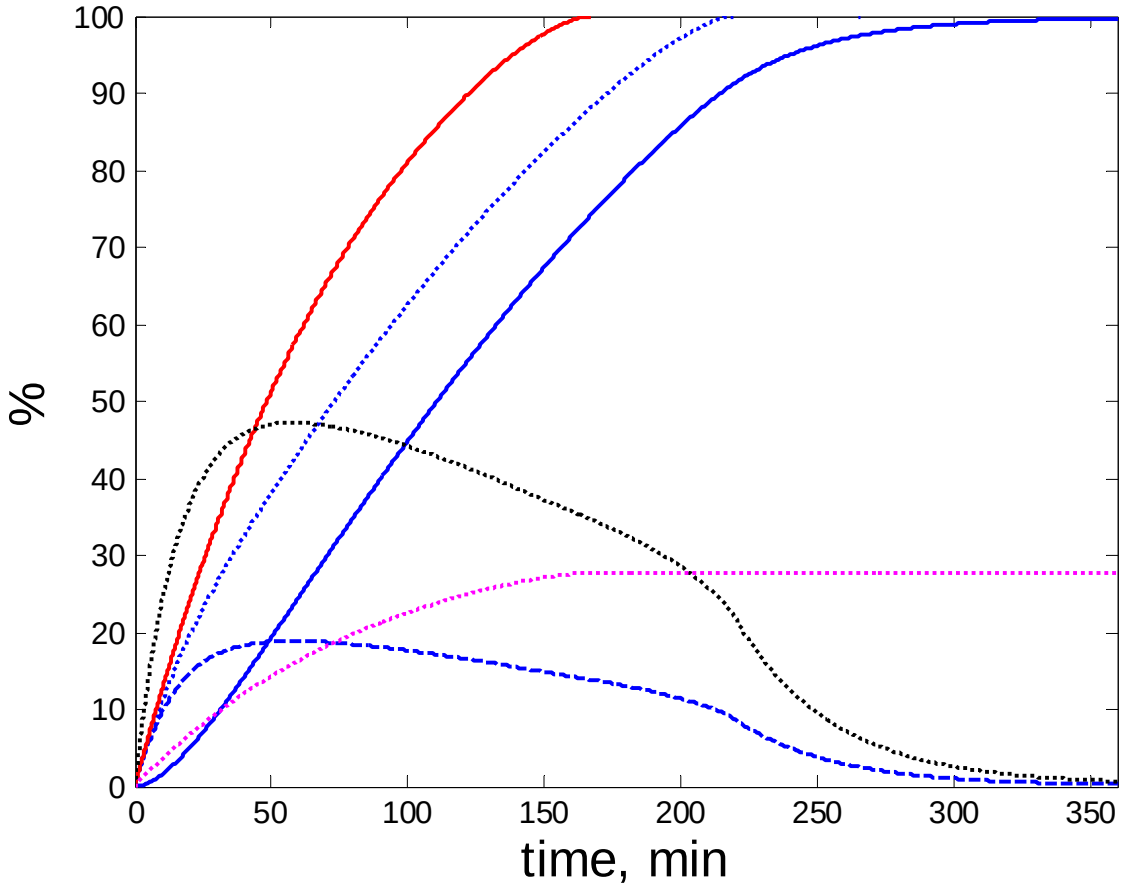
(Dose number = 1)

A/V = 2.3

Vw = 100 mL

Two phase physiologic dissolution model

P_m= 2 x 10^{-4} cm/sec, particle radius = 50 µm



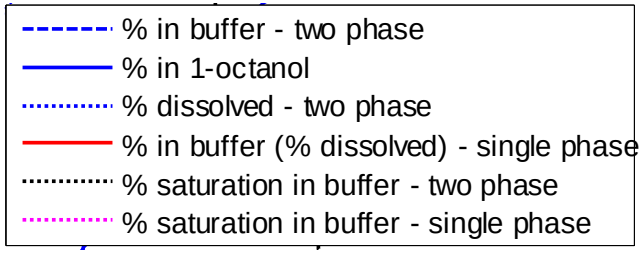
BCS Class II

Sol=100µg/mL Dose = 25 mg

(Dose number = 1)

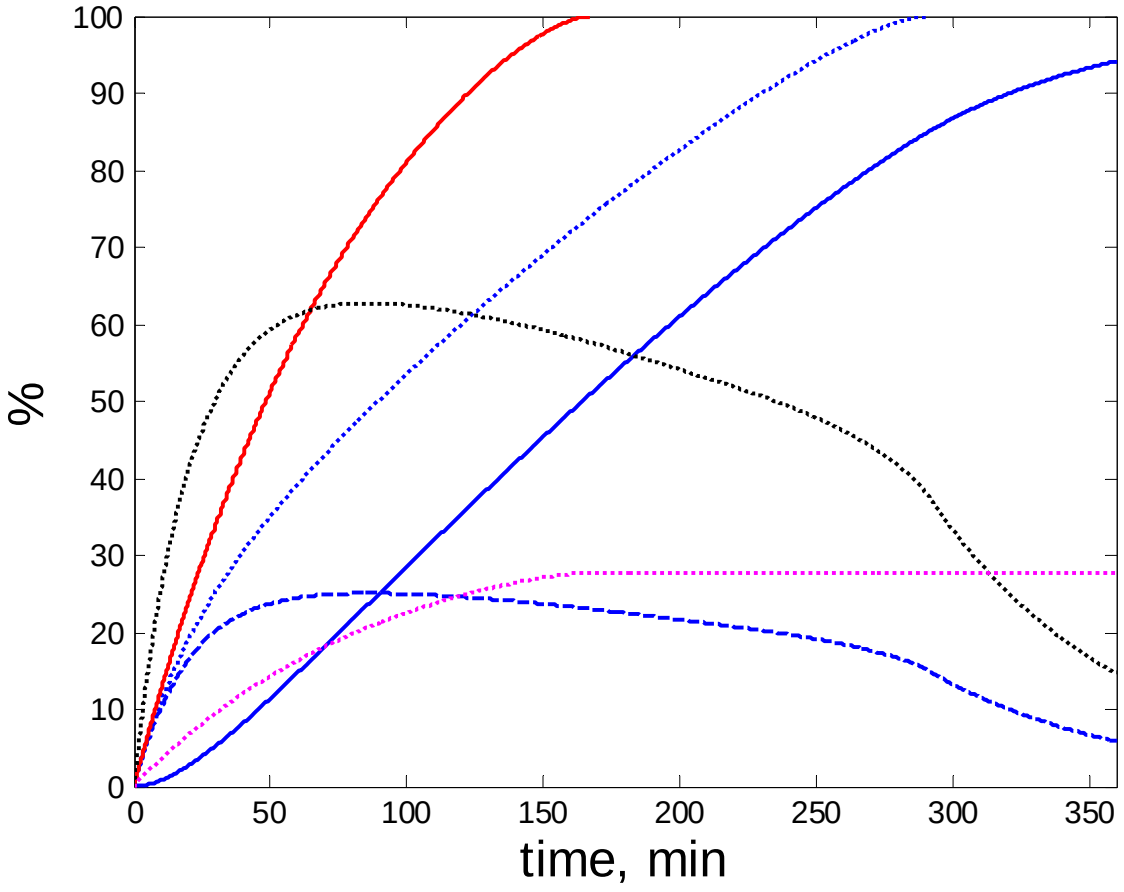
A/V = 2.3

Vw = 100 mL



Two phase physiologic dissolution model

P_m= 1 x 10^{-4} cm/sec, particle radius = 50 µm



BCS Class II

Sol=100µg/mL Dose = 25 mg

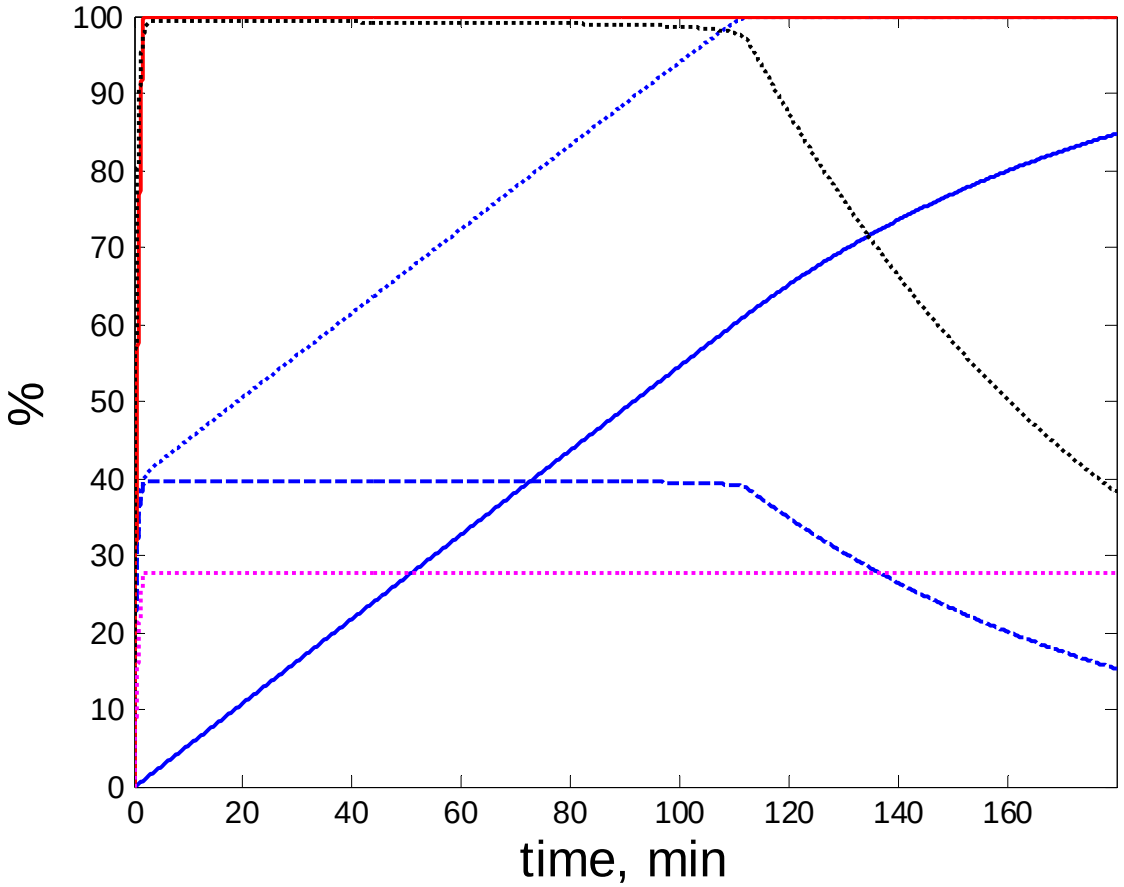
(Dose number = 1)

A/V = 2.3

Vw = 100 mL

Two phase physiologic dissolution model

P_m=1x10^{-4} cm/sec, particle radius = 5 µm



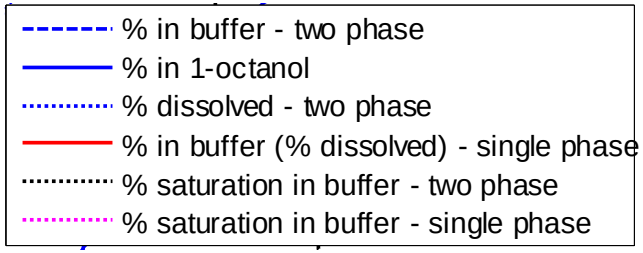
BCS Class II

Sol=100µg/mL Dose = 25 mg

(Dose number = 1)

A/V = 2.3

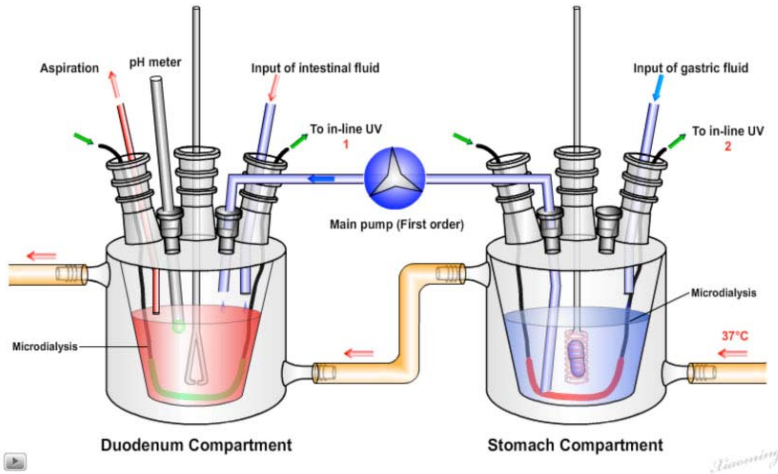
Vw = 100 mL

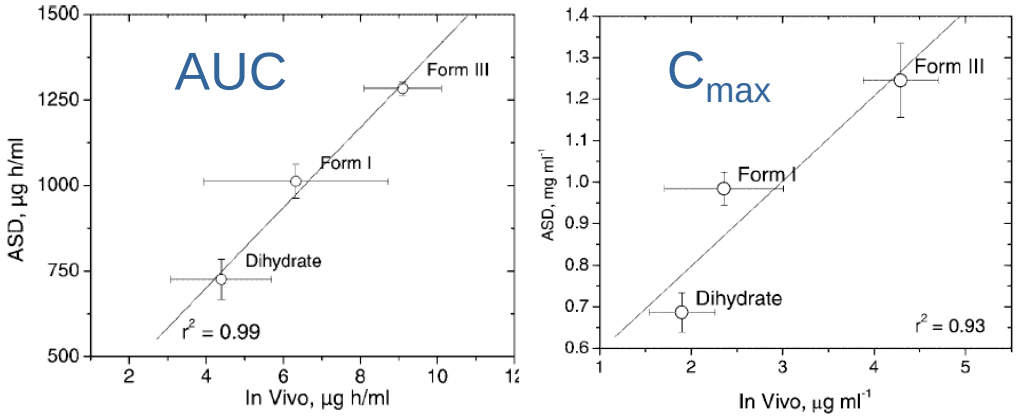


Stomach and intestine: Two-compartment dissolution apparatus

- Several publications in literature describing Artificial Stomach-Duodenum (ASD)
- Used in pharmaceutical industry
- Used to compare ASD performance with *in vivo* bioavailability values

Relative bioavailability estimation of carbamazepine crystal forms





SRCarino, DCSperry, MHawley. JPharmSci 95:116-125 (2006).

Impact of stomach pH on Oral Absorption of Anticancer Agents

Table 3 Effect of acid-reducing agents on the oral absorption of targeted anticancer agents

Drug (dose)	Acid-reducing agent	Mean change AUC	Mean change C_{max}	Subjects	Comments
Dasatinib (50 mg)	Famotidine (40 mg) 10 hours prior to dasatinib Famotidine (40 mg) 2 hours after dasatinib	↓61% ↔	↓63% ↔	Healthy subjects	AUC_{0-12}
Dasatinib (50 mg)	Maalox 30 ml 2 hours prior to dasatinib Maalox 30 ml coadministered with dasatinib	↔ ↓55%	↑26% ↓58%	Healthy subjects	AUC_{0-12}
Dasatinib (100 mg)	Omeprazole (40 mg) daily for 5 days and on day 5 with dasatinib	↓43%	↓42%	Healthy subjects	AUC_{inf}
Erlotinib (150 mg)	Omeprazole (40 mg) daily for 7 days	↓46% ↓58%[a]	↓61% ↓69%[a]	Healthy subjects	Primary metabolite[a]
Erlotinib (150 mg)	Ranitidine 300 mg daily for 5 days and erlotinib 150 mg single dose 2 hours after ranitidine dose on third day	↓33%	↓54%	Healthy subjects	
Erlotinib (150 mg)	Ranitidine 150 mg b.i.d. for 5 days and erlotinib 150 mg single dose 2 hours before and 10 hours after ranitidine on third day	↓15%	↓17%	Healthy subjects	
Gefitinib (250 mg)	Two oral doses of 450 mg ranitidine (13 hours and 1 hour before 250 mg of gefitinib) followed by sodium bicarbonate to maintain gastric pH above 5 for 8 hours	↓44%	↓70%	Healthy subjects	
Imatinib (400 mg)	Omeprazole (40 mg) daily for 5 days and on day 5 with imatinib	↔	↔	Healthy subjects	
Imatinib (400 mg)	Maalox Max (20 ml) 15 minutes before imatinib	↔	↔	Healthy subjects	
Lapatinib (1,250 mg)	Esomeprazole (40 mg) daily for 7 days at bedtime	↓26%	NA	Cancer patients	
Nilotinib (400 mg)	Esomeprazole (40 mg) daily for 6 days and on day 6 with nilotinib	↓34%	↓27%	Healthy subjects	
Axitinib (5 mg)	Rabeprazole (20 mg) q.d.	↓15%	↓40%	Cancer patients	

AUC, area under the curve, C_{max}, peak plasma concentration; NA, not applicable.

[a]Primary metabolite data.

Ref: N.R. Budha, A. Frymoyer, G.S. Smelick, J.Y. Jin, M.R. Yago, M.J. Dresser, S.N. Holden, L.Z. Benet, and J.A. Ware. Clinical Pharmacology & Therapeutics (2012).

Advantages & disadvantages of two-compartment systems

Advantages

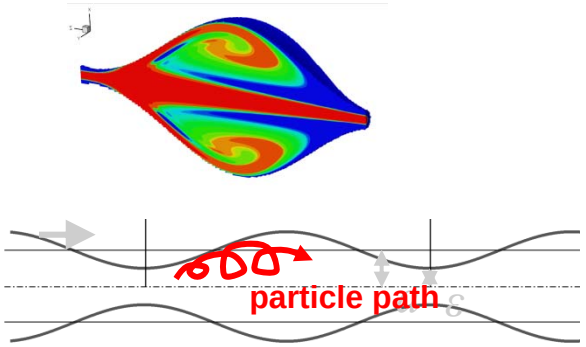
- Sequentially exposes drug to gastric followed by intestinal media
  - Differing media properties in stomach and intestine (e.g. pH, lipid & bile salt concentrations) can affect dissolution
- Captures *in vivo* gastric-emptying rates and flow rates
  - Can vary to simulate effect on dissolution
- Potential to integrate peristaltic motion

Disadvantages

- Does not contain separate phase/chamber for absorption
  - Assumes dissolved drug proportional to drug in plasma

Topics

- Where are we now?
- What opportunities are there (there are many)?
  - GI physiology
    - Fluid volume
    - Hydrodynamics
    - Buffer (bicarbonate)
  - Advanced dissolution methods
    - Two phase systems (simulating dissolution and absorption)
    - Two compartment systems (simulating stomach and intestine)
  - Computational Tools
    - Fluid Dynamics
    - Dissolution
    - Absorption Modeling



Exciting research is going on….

Motility and Absorption in the Small Intestine

Quantification of Small Bowel Water/Physiology

Coupling Biorelevant Dissolution Testing with PBPK Modeling

Modeling Hydrodynamics in the Intestine

Bicarbonate Buffer and Surface pH

In Vitro Dynamic Lipolysis Model

Precipitation Kinetics of Poorly Soluble Drugs under Supersaturated State and Precipitation Inhibitors

Rotating Disk as a Dissolution Tool

Artificial Stomach Duodenum (2 compartment dissolution)

Miniscale Dissolution-membrane Partitioning System

Two Phase Dissolution System

Two Compartment Caco2 model /Mini-scale Dissolution

In vivo and computational biopharmaceutical aspects of precipitation and intestinal permeability

Dynamic Dissolution (TIM-1)

Methods for Estimation of Biorelevant Drug Solubility

Combining Experimental and Computational Approaches for Predicting Oral Bioperformance

Future Direction and Research Needs

- Enhanced Understanding In Vivo environment (human, animal)
  - Hydrodynamics
  - Volume
  - Gastric Emptying
  - Fluid content, buffer
- Development of Relevant In Vitro Methodologies
  - Likely not one-size-fits-all
  - Address/simulate dissolution and absorption kinetics
  - Precipitation assessment / inhibition
  - Modified / Delayed Release optimization
  - Development of Advanced Computational Tools (In Vitro & In Vivo)
  - Hydrodynamics
  - Dissolution
  - Absorption
  - Metabolism
- Application of physicochemical principles to dissolution
-
-

Questions/discussion

Dissolution Testing and Quality-by-Design

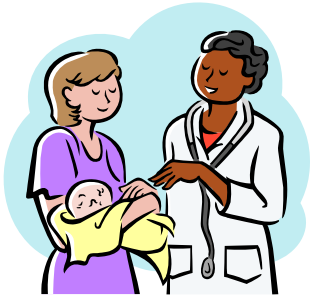
Lawrence X. Yu, Ph. D.
Deputy Director for Science and Chemistry
Office of Generic Drugs
Food and Drug Administration

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

Quality-by-Design

- ICH Q8(R2)
  - Pharmaceutical Quality-by-Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management
- Quality-by-Design Tools
  - Prior knowledge
  - Risk assessment
  - Design of experiments and data analysis
  - Process analytical technology (PAT) tools

QbD: Linking Process/Product /Patient



Patient

Product

Process

Quality Target Product Profile

Critical Quality Attributes

Material Attributes & Process Parameters

Quality Target Product Profile (QTPP)

- QTPP
  - A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality (performance)
- Guide to establish product design strategy and keep product development effort focused and efficient

What Does QTPP Include?

- Intended use in clinical setting
  - Route of administration, dosage form (delivery systems), and container closure system
- Quality attributes of drug product
  - Appearance, Identity, Strength, Assay, Uniformity, Purity/Impurity, Stability, and others
- Active pharmaceutical ingredient release or delivery and attributes affecting pharmacokinetic characteristics (safety and efficacy)
  - Dissolution, aerodynamic performance, etc.

Dissolution and QbD

- Dissolution can be used to help relate the "Product" to the "Patient" in the QbD paradigm
  - Relate *in vivo* performance of a drug to *in vitro* measurements
  - Enable development of clinically relevant specifications
  - Understand the impact of formulation and manufacturing process variations
- Clinically meaningful dissolution specifications that assure consistent therapeutic benefit can aid manufacturing control strategy development

Roles of Dissolution Testing

- A quality control tool
  - Batch-to-batch consistency
  - Provide quality assurance
- An *in vitro* surrogate for product performance
  - Formulation development
  - Bioequivalence studies

Dissolution for Quality Control

- A product specific quality control test
  - The hydrodynamics and medium for this test are chosen for reproducibility and detection of product changes
  - The design of this test is not constrained by a desire to mimic *in vivo* conditions
  - Acceptance criteria for consistency of batches

Dissolution for *In Vivo* Performance

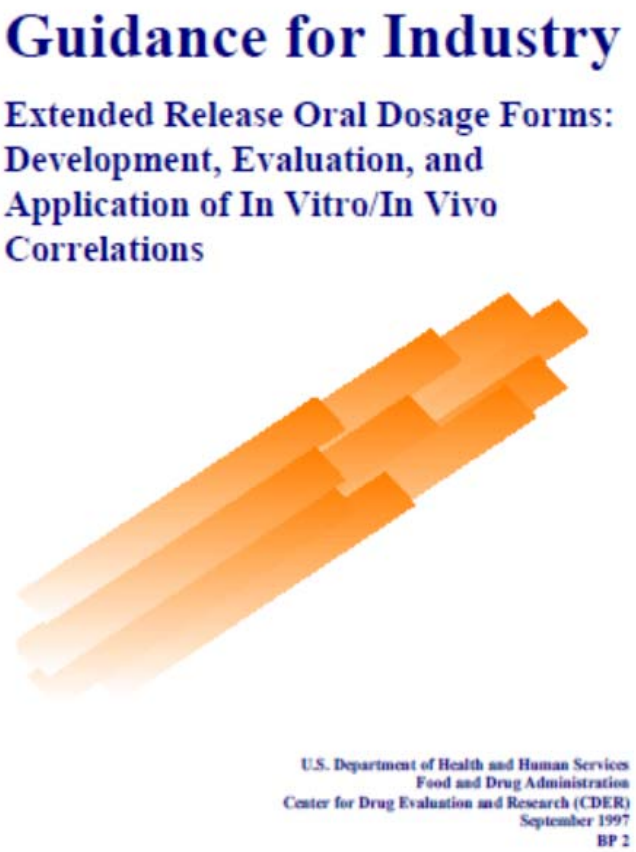
- A biorelevant dissolution test
  - Correlates with *in vivo* dissolution
    - The hydrodynamics and medium for this test are chosen to reflect *in vivo*
    - Biorelevant dissolution test is a one-time test to provide a baseline for product performance

Predictive Dissolution Enables Efficient Product Development

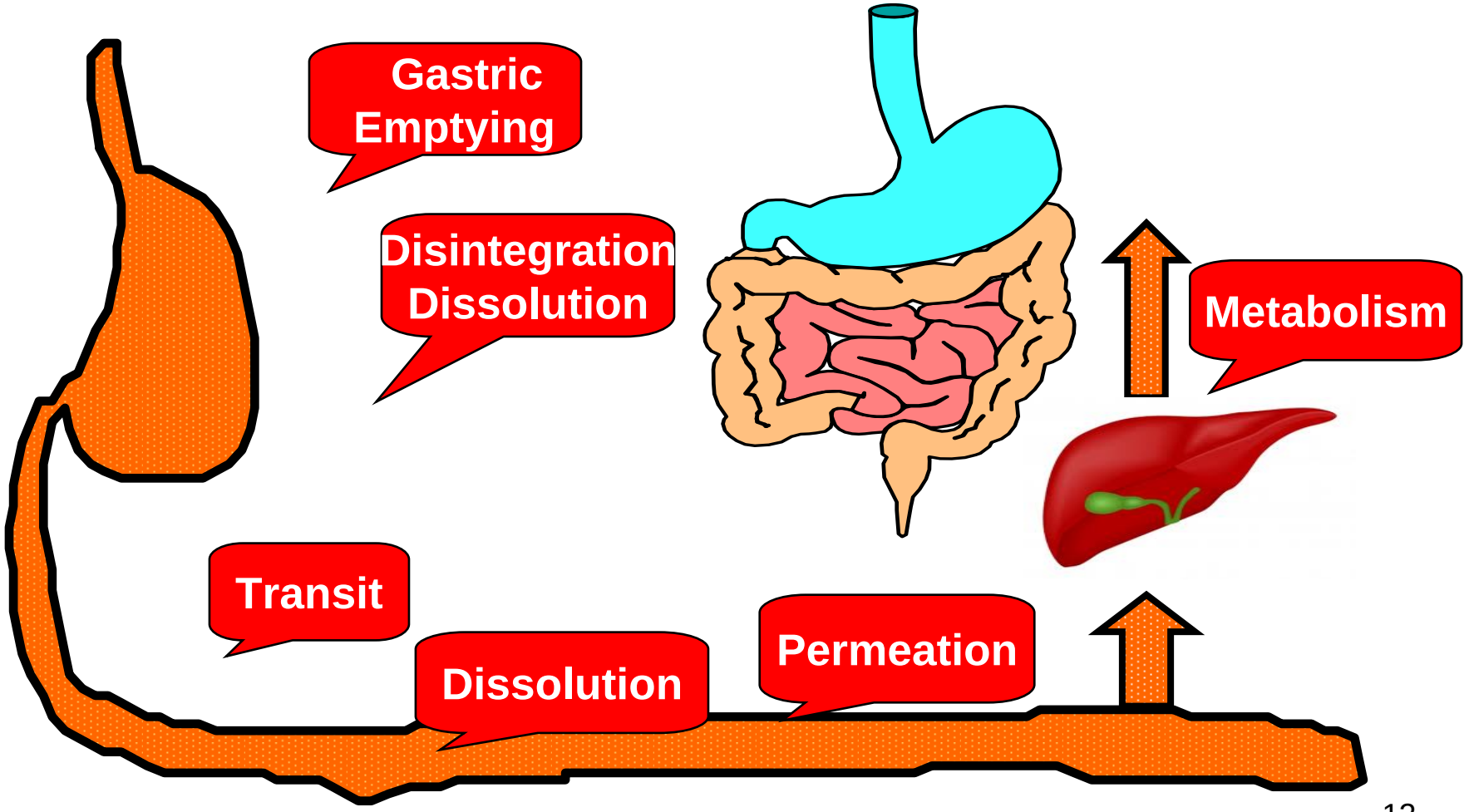
- It is unrealistic to conduct *in vivo* bioequivalence studies for every formulation and manufacturing change during pharmaceutical development or for every post-approval change
- Predictive dissolution can streamline product development and lead to time and cost savings during product development while enhancing the significance of *in vitro* testing

FDA IVIVC Guidance

- IVIVC = in *vitro-in vivo* correlation
- Contents
  - Data/formulation requirements
  - Predictability evaluation
  - Application in waivers of in vivo bioequivalence studies and dissolution specifications (pre- and post-approval)



Oral Drug Absorption Process



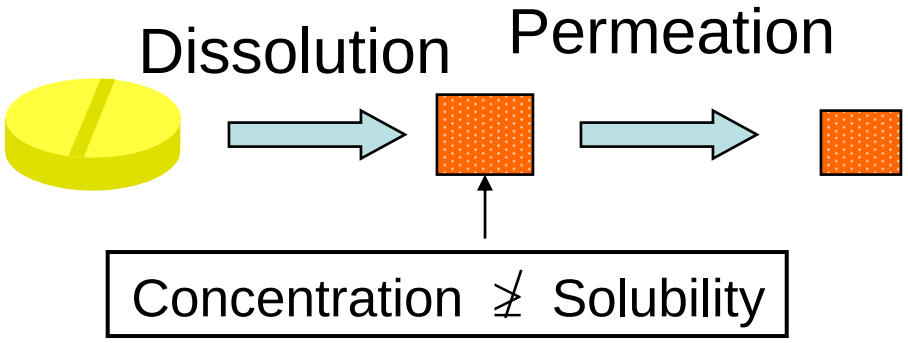
Limits to Oral Drug Absorption

- Gastric emptying
- Dissolution
  - DS dissolution rate = D *S/h (C_s - C_l)
    - D - diffusion coefficient
    - S - dissolution surface area : **Drug substance**
    - h - Aqueous boundary thickness
    - Cs - Solubility: **Drug substance**
    - Cl - Concentration in dissolution media
- Permeability: **Drug substance**

In Vitro and *In Vivo* Relationship

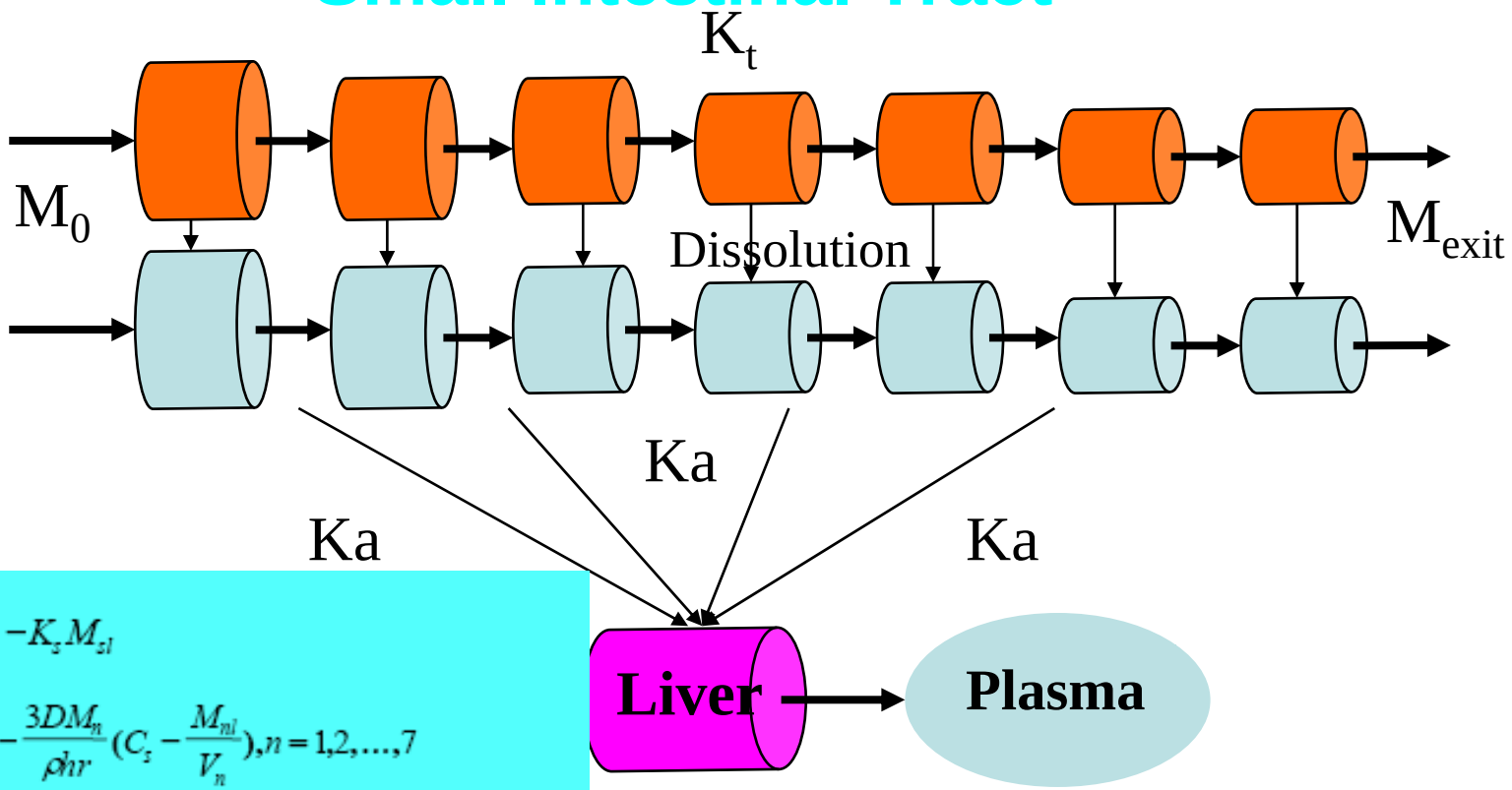
- Limits to oral drug absorption
  - Dissolution-limited
  - Solubility-limited
  - Permeability-limited

$$\frac{dM}{dt} = \frac{D}{h} S (C_s - C)$$



The CAT Model

Small Intestinal Tract



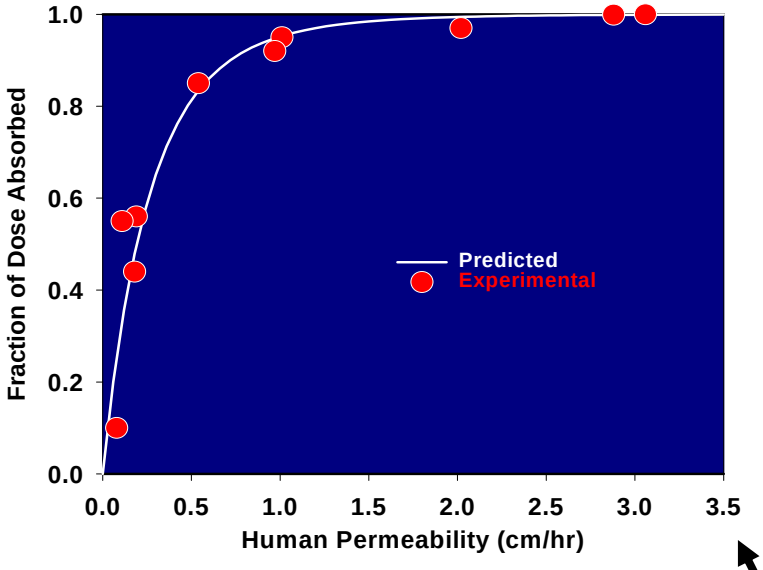
$$\frac{dM_{ss}}{dt} = -K_s M_{ss} \qquad \frac{dM_{sl}}{dt} = -K_s M_{sl}$$

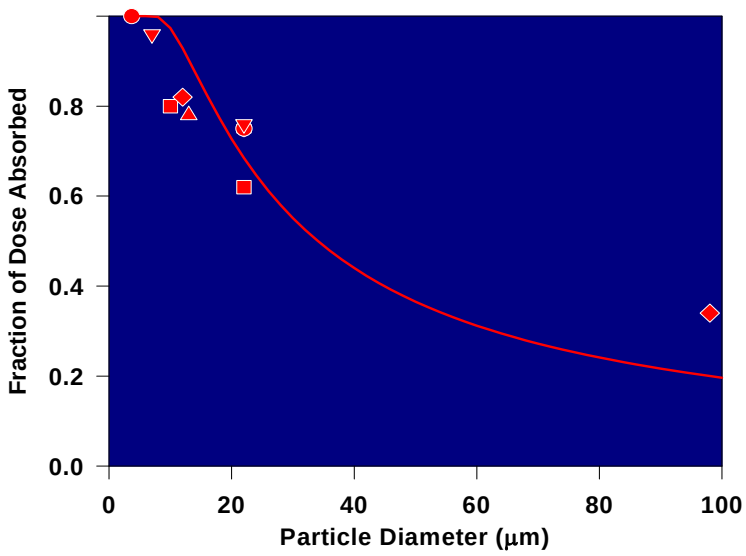
$$\frac{dM_{ns}}{dt} = K_t M_{(n-1)s} - K_t M_{ns} - \frac{3DM_n}{\rho hr}(C_s - \frac{M_{nl}}{V_n}), n = 1,2,\ldots,7$$

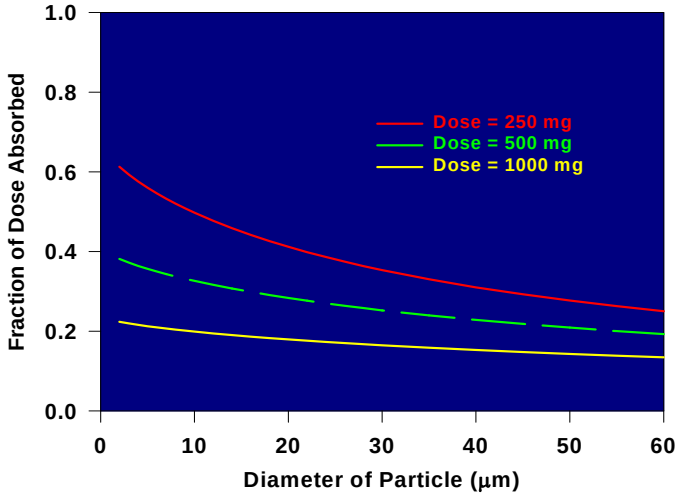
$$\frac{dM_{nl}}{dt} = K_t M_{(n-1)l} - K_t M_{nl} - \frac{2P_{eff} M_{nl}}{R} + \frac{3DM_{ns}}{\rho hr}(C_s - \frac{M_{nl}}{V_n}), n = 1,2,\ldots,7$$

$$\frac{dM_a}{dt} = K_a \sum_{n=1}^{7} M_{nl} \qquad F = F_a \bullet F_h = F_h \lim_{t\to\infty} M_a / M_0 = \frac{F_h}{M_0} \int_0^\infty K_a \sum M_{nl} dt$$

Predicting Oral Absorption







Dissolution-limited

Permeability-limited

Solubility-limited

Biopharmaceutics Classification System

Amidon, et al., *Pharm. Res.,* 1995

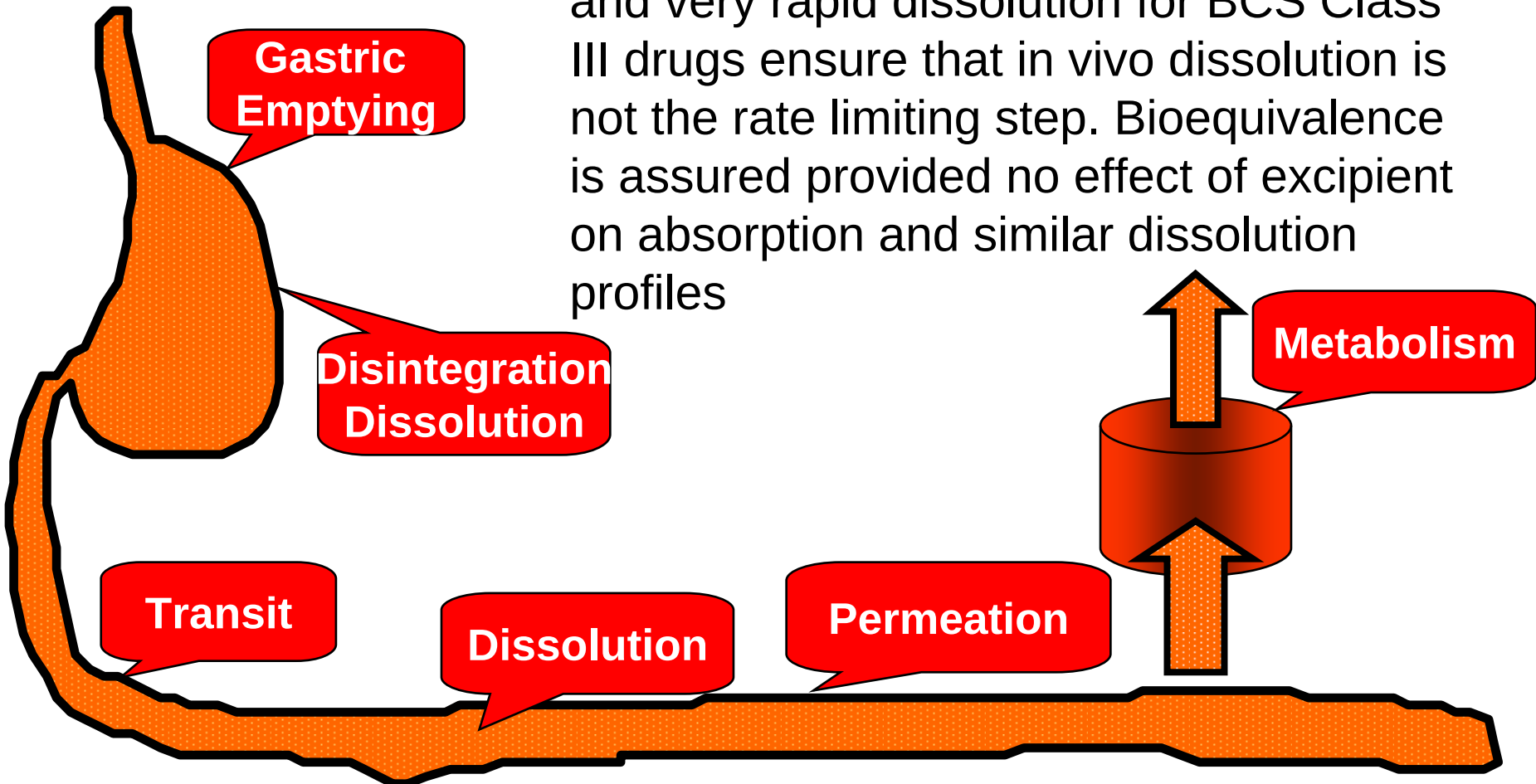
- The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability.

Biopharm. Class	***Solubility***	***Permeability***
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

- The understanding of drugs based on BCS can aid in formulation and manufacturing development in a QbD paradigm.

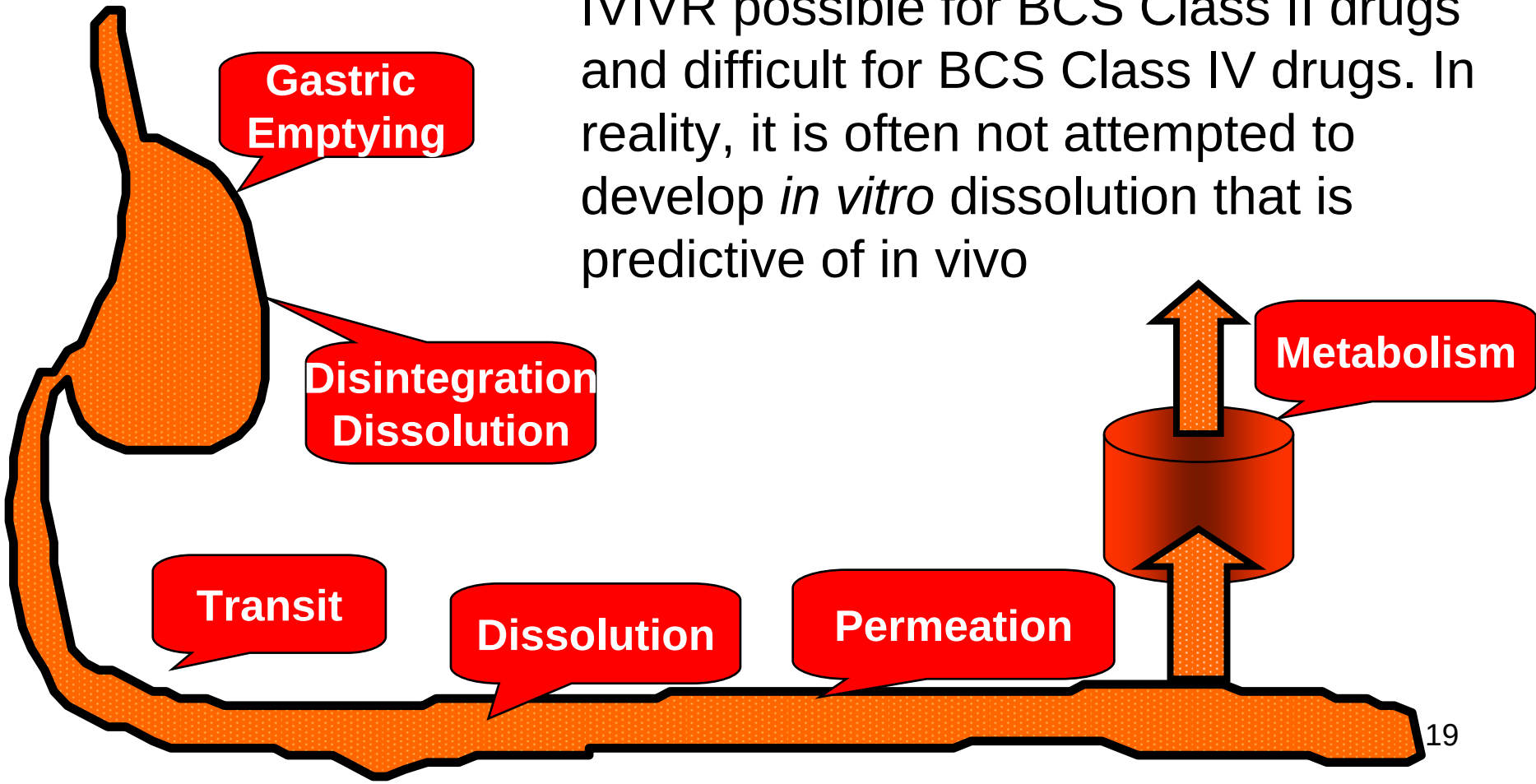
BCS Class I and III Drugs

Rapid dissolution for BCS Class I drugs and very rapid dissolution for BCS Class III drugs ensure that in vivo dissolution is not the rate limiting step. Bioequivalence is assured provided no effect of excipient on absorption and similar dissolution profiles



BCS Class II and IV Drugs

IVIVR possible for BCS Class II drugs and difficult for BCS Class IV drugs. In reality, it is often not attempted to develop *in vitro* dissolution that is predictive of in vivo



BCS Class I

- BCS Class I drugs formulated in an immediate release dosage forms
  - No bioequivalence studies may be needed for developing “predictive” dissolution
  - Rapid dissolution may be used for formulation development and establishment of design space
  - Rapid dissolution for BCS Class I drugs in immediate release dosage forms may be used to justify formulation and manufacturing changes

BCS Class II

- BCS Class III drugs formulated in an immediate release dosage forms
  - No bioequivalence studies may be needed
  - Very rapid dissolution may be used for formulation development and establishment of design space
  - Very rapid dissolution for BCS Class III drugs in immediate release dosage forms may be used to justify manufacturing changes
  - Excipient effect needs to be further investigated

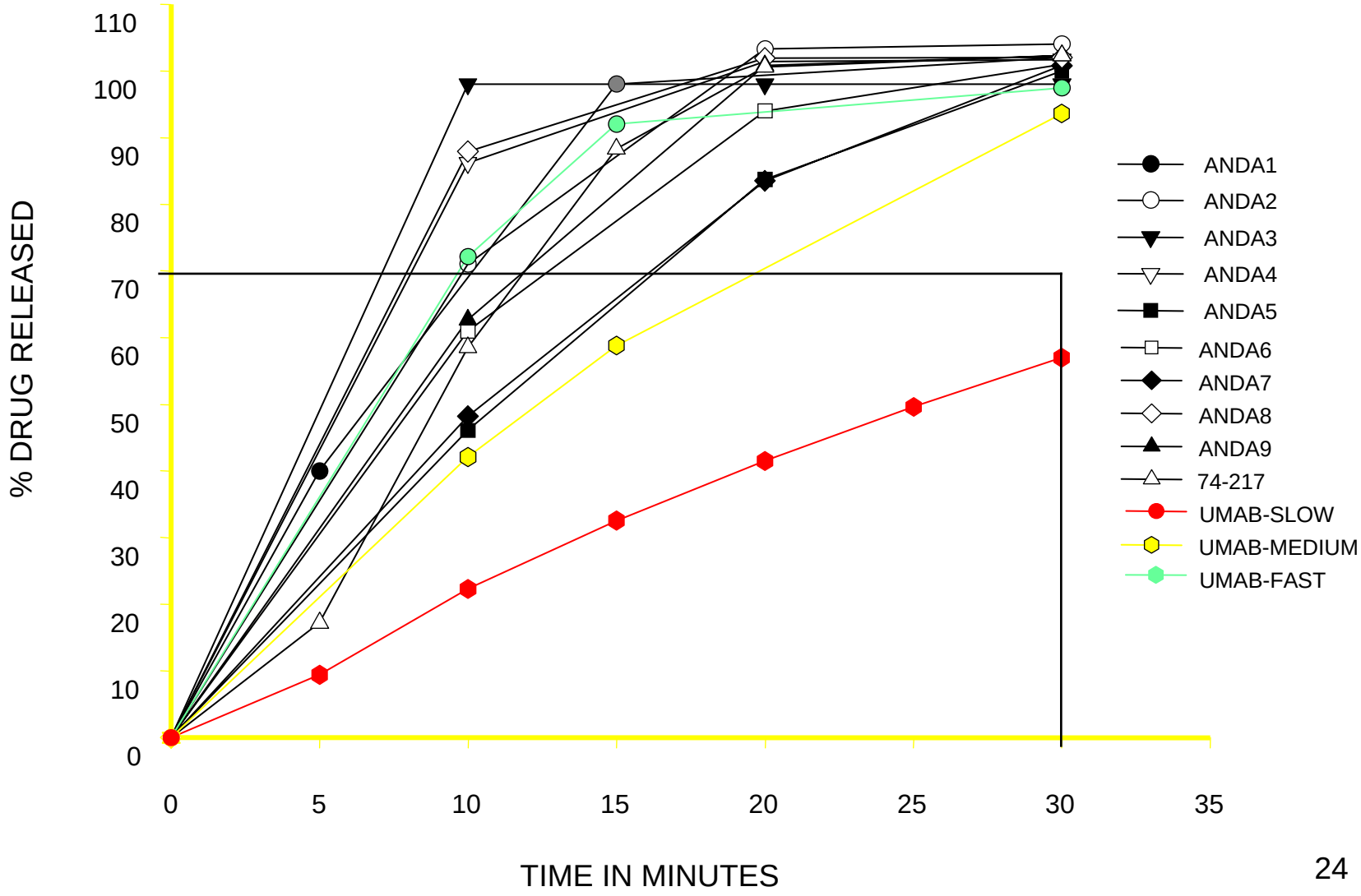
BCS Class II and IV

- BCS Class II and IV drugs formulated in an immediate release dosage forms
  - Bioequivalence studies are most likely needed to develop predictive dissolution
  - Predictability of biorelevant dissolution should be further explored and investigated

Extended-release Dosage Forms

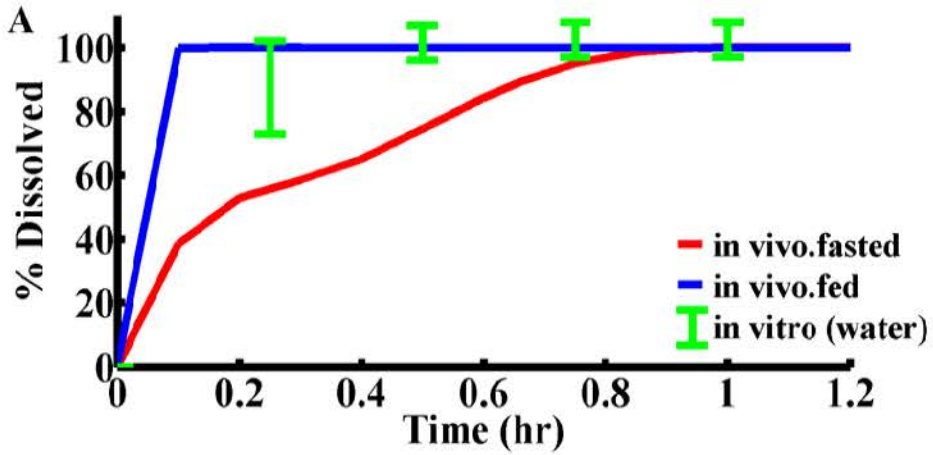
- Extended-release Dosage Forms
  - Bioequivalence studies are likely needed to establish IVIVC/IVIVR and develop predictive dissolution
  - Predictive dissolution can then be used to support establishment of a design space
  - IVIVC/IVIVR can be used to support manufacturing changes

Dissolution for a BCS Class I Drugs

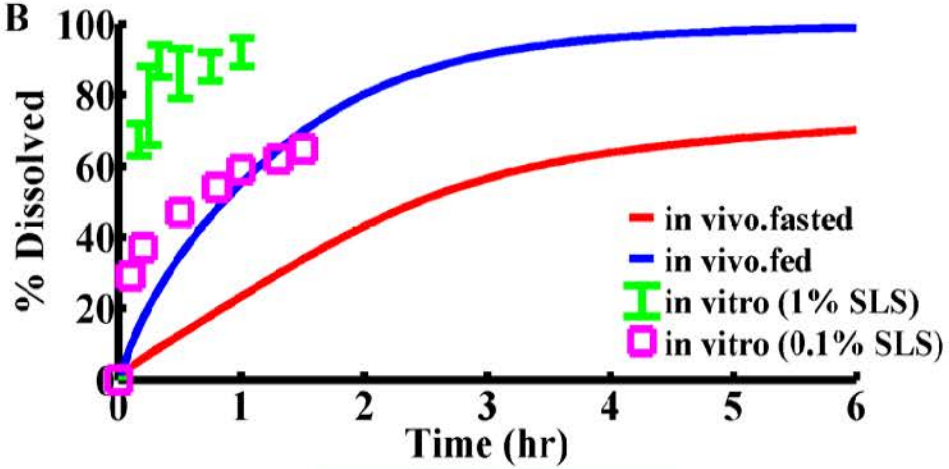


In Vitro vs. *In Vivo* Dissolution

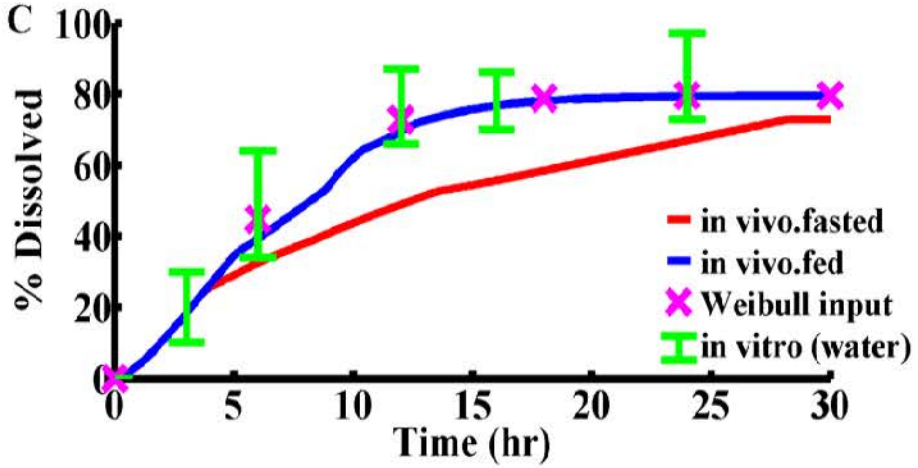
IR suspension



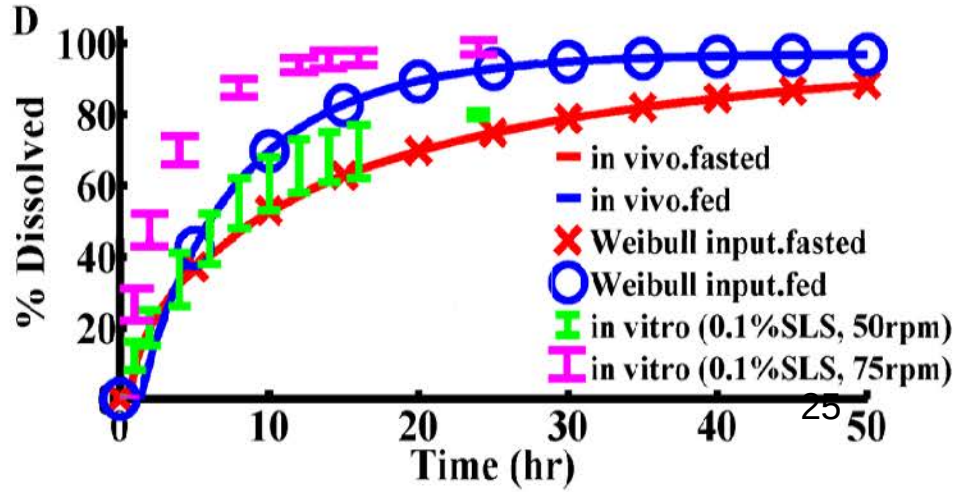
IR tablet



XR tablet



XR capsule



Future Directions

- Application of the QbD approach has the potential to bridge the gaps between in vitro measurements and *in vivo* performance
  - A science based approach incorporating studies both in the laboratory and clinic
  - Utilization of advanced dissolution methodologies for predictive dissolution
- Other approaches other than IVIVC/IVIVR are possible that provide increased product and process understanding

Conclusions

- There are many tools related to dissolution that can aid in implementation of QbD
  - Biorelevant dissolution methods, which may utilized advanced apparatus and/or media
  - Predictive dissolution modeling
  - IVIVC or IVIVR studies
- All of these tools can aid product quality
  - Enhanced product and process understanding
  - Clinically relevant specifications